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Mathematical Sciences

Progress in the Mathematical Modelling of Developmental Processes in Biological Systems, since Publication of *On Growth and Form* by D'Arcy W. Thompson

by

Brian H. Bonney

Thesis for the degree of Master of Philosophy

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ABSTRACT

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PROGRESS IN THE MATHEMATICAL MODELLING OF DEVELOPMENTAL PROCESSES IN BIOLOGICAL SYSTEMS, SINCE PUBLICATION OF *ON GROWTH AND FORM* BY D'ARCY W. THOMPSON

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In his renowned book *On Growth and Form*, first published in 1917, D'Arcy Wentworth Thompson stressed the significance of physical laws and mechanisms in determining the development of form and pattern in living organisms. This was at variance with the view held by the majority of his contemporaries in Biology, that natural selection and evolution were the primary factors involved in driving these processes. This disparity of views was understandable in Thompson's day, given that most biologists of the time were (at least implicitly) vitalists.

Now, given a general acceptance that the phenomena of life are subject to the laws of physics and chemistry, Thompson's ideas are seen as complementary to the processes of evolution by natural selection. Yet, Thompson's viewpoint still finds itself marginal to present day thinking in developmental biology, in that his ideas emphasise the significance of physical, more than biochemical and genetic processes. In particular *On Growth and Form* highlights the role of minimisation principles, and of formal symmetries of one type or another in developmental phenomena. Although these are manifestly of great significance to a full understanding of developmental systems, such principles are still not central to the attention of experimentalists in mainstream research.

I conclude that Thompson, in the early 20th Century, could not quantify biology, because neither enough biology, nor enough of the underlying physics and chemistry, were yet understood. Even if they had been, the mathematical tools available at the time were inadequate. The real revolution has come with the advent of high performance computing, enabling the complexities with which Thompson aspired to grapple, to be studied meaningfully.

A Note on Some Conventions Used in the Writing

For economy of space, paraphrasing of quotes from D.W.Thompson and other authors cited will be the norm henceforward. Any changes in wording, or deleted parts of text will be indicated respectively within [square brackets] and with ... *ellipses* ... like so. Unless otherwise stated, any *italicised* emphases within quotations are my own, and not the cited authors'. All citations from *On Growth and Form* are from the first edition (1917), unless otherwise stated. If a particular citation used can only be found in the second edition (1942), then this will be made clear. *On Growth and Form* in the general sense is referred to as 'OGF', and the first and second editions are referred to respectively as 'OGF(1)' and 'OGF(2)'.

Passages in **bold** are there to point out links between successive Chapters and/or sections and subsections within chapters. Short statements in ***bold/italic*** are there to cross-reference material, usually by section or page numbers, within or between chapters. Any words or phrases shown in *italic* are technical terms, usually appearing at the first occurrence of the term in the text.

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Declaration of Authorship

I, Brian H. Bonney, declare that the thesis entitled *Progress in the Mathematical Modelling of Developmental Processes in Biological Systems, since Publication of* On Growth and Form *by D'Arcy W. Thompson* and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- parts of this work have been published as:
  - None of my own material from this Thesis has so far been published. If published material from other authors is cited or quoted, then this is made clear in the text.

Signed: ....

Date: ....

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Thanks also to Seth Bullock, Jason Noble and their colleagues and students in the Southampton Complex Systems Simulation DTC, for reintroducing me to study habits, before my moving to Mathematical Sciences in 2013. I am also grateful to the many students, with whom I have shared working space (though not necessarily academic interests) over the years. Some particularly worthy of mention are: Guy Jacobs and Gereon Kaiping in Mathematical Sciences; and Ariana Stylianidi Christodoulou, William Woodhead and Joan Garcia Tormo in the String Theory Group. I could not have managed without their help in attempting to master the IT skills and practices that did not exist in my days of study prior to the 1980s.

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CHAPTER 1

Introduction

In view of the recent centenary of the publication in 1917 of D'Arcy Thompson's Book *On Growth and Form*, here referred to henceforward as OGF, it seems timely to review the elaboration of our understanding of developmental processes in living organisms since Thompson's time, and to assess the significance of his contributions to this history.

After a very brief introduction to Thompson's life and career, we will consider the philosophical principles that influenced his thinking in the programme of research he put forward in the book. The descriptively-based mathematical biology advocated by Thompson, along with his own Theory of Transformations, are then placed in the context of progress with the more empirically-based theories of development elaborated in the period 1917 to 1942, between the publication of the two editions of OGF - respectively referred to here as OGF(1), and OGF(2). We show how the vague concept of the gene as a basic agent of inheritance became refined to incorporate genes as developmental agents. Subsequently, the gene concept is elaborated further, to establish ideas of genetic control and regulation, leading on to genetically programmed development. The vital importance of molecular biology is discussed in this context.

We then link these increases in empirical knowledge to concurrent theoretical developments, which have underpinned and enhanced our understanding of organismic development. The significance of Systems Theory and Cybernetics, along with their offshoots - Information Theory, and the various forms of finite state modelling such as Automata

Theory and Formal Languages, are brought into the picture here. All of this culminates in the centrality of Complexity Theory and Complex Networks to current day approaches adopted for research into Developmental Systems. We relate all this to the contemporary synthesis, attempt to identify key trends in Developmental Biology, and how the above history, including Thompson's contribution, has spawned areas of research that are the foci of activity today.

1.1 A Brief Introduction to Thompson's Life and Career

The single most authoritative account of the life and work of D'Arcy Thompson, is the book *D'Arcy Wentworth Thompson; The Scholar Naturalist, 1860-1948* published in 1958 by his daughter Ruth D'Arcy Thompson [1].

Thompson, Fig.1.1.1, was a classic Victorian polymath with academic interests of an extraordinary breadth. Educated in Natural Sciences and other subjects at Trinity College Cambridge, he was by 24 already a professor of biology at University College Dundee. There he remained until 1917, when he transferred to a chair at the University of St Andrews, where he continued in post until his death in 1948 at the age of 88. On the way he accumulated honours galore, including fellowships of the Royal Societies of Edinburgh (1885) and of London (1916), and a knighthood (1937). His publication record stretched over almost seventy years, between 1879, and 1945, comprising some 300 items, some concerned with biology and natural history, some with the classics, along with ventures into the application of mathematics to the biological sciences (ultimately leading to *On Growth and Form*, which we will henceforth abbreviate to OGF) for which Thompson is justly famous.

The original 1917 version of *On Growth and Form* [2], referred to below as OGF(1), comprised a 'mere' 793 pages, concerning learned aspects of mathematics and physics as applied to biology. The initial limited print run of 500 copies would only be exhausted in 1923, at which point a second edition was requested. But Thompson was a busy man, and a perfectionist, so the second, revised edition, comprising an even bulkier 1116 pages, did not appear until 1942 [3] (referred to below as OGF(2)). Both editions are freely available on the web.

The 1942 edition, though much expanded, still retained the opening comment (from the 1917 edition) that the whole work should be considered merely as a preface. This reflects the fact that there was nothing fundamentally new as compared to the first edition, but that the additional space was filled by many more examples illustrating the messages

Figure 1.1.1: From the Frontispiece of [1], 'D'Arcy Thompson holding a nautilus shell (the last photograph)'

Thompson wished to convey. To many readers this meant that the new edition was harder to read, and the fundamental ideas were obscured by a surfeit of new material, which collectively provided no new unifying principles, just a treasure trove of examples. Hence, the reviews of the 1942 edition were mixed and, overall, the book can be regarded as having had a somewhat temperate reception.

A 1952 article in *Scientific American* [4] by the up-and-coming Princeton biologist John Tyler Bonner opines that OGF is 'a depository of original ideas that have influenced developmental biology', and that it is 'a work of literature whose style has few peers in the field of biology'. Because of this, avers Bonner, it 'is frequently condemned or dismissed by experimental scientists'. So Bonner aspired to produce a version of OGF, which could appeal to experimental biologists. Thus the abridged edition appeared in 1961 [5], edited by Bonner, containing a digestible summary of only 346 pages. This is the edition normally used by contemporary scholars.

Before considering further the content of his book (and how it might be seen, by accident or design, to reflect actual progress made - over the last 100 years - in empirical and theoretical studies in the developmental sciences) let us turn briefly to some key messages which Thompson attempted to get across in OGF.

1.2 Thompson's Programme as Enshrined in 'On Growth and Form'

Publication of Charles Darwin's *On the Origin of Species* in 1859 [6], led ultimately to the acceptance by almost all biologists, that the Theory of Evolution by Natural Selection, and of the genetics that describes how the process works at the macroscopic, microscopic, and (more recently) the molecular and nanoscopic levels - the so-called *Neo-Darwinian Synthesis* - should be a central organisational tool for biological understanding. It was not so much that Thompson was *against* Natural Selection. Rather, he was sceptical that this was the whole story. Already in 1894, a note from him in *Nature* had been entitled *Some Difficulties in Darwinism* [7]. By 1917 his position had hardened, and OGF elaborates his arguments further. Darwin and Alfred Russel Wallace [8] had ascribed to common descent alone, the origin of the homologies enabling the classification of organisms into a 'Tree of Life'. But Thompson paid more attention to the demands of physical law (rather than to common descent, or the transmission of heritable characteristics) stating in his own words (OGF(1), p251): 'But this generalisation is apt in my opinion to carry us too far'.

An excellent review and critique of OGF was provided by J.T.Bonner in his Editor's Introduction to the abridged edition of OGF [5]. This includes the following interpretation of how the persistent importance of the book has come about:

'... D'Arcy Thompson was consistently able to examine subjects of significance in biology from a fresh point of view, and the mere fact that there was another point of view (sometimes one first imagined in antiquity) comes as a shock, and therefore a stimulus, to those who so easily fall into scientific fads and fashions of our day, and make little effort to look beyond the horizons of the "current views". The most conspicuous attitude in the book is the analysis of biological processes from their mathematical and physical aspects. ... Except for the details of some specific analyses, the general approach, in this day of biophysics, mathematical biology, cybernetics, etc., is hardly novel, although it must be remembered that it was very much so in 1917 at the time of the first edition'.

(***For another, more generalised view of the continued appeal of Thompson's book to a broader readership, see section 3.2, p50, and the citation from E.F.Keller.***)

It is in this spirit that I wish to put forward a clarification of exactly what was stated in OGF, and to outline in, I hope, plainer and more current language than Thompson's own, something about the programme enshrined in the book. So let us take our lead from Thompson himself, who discusses the details of

his approach throughout OGF, but in particular in his *Introductions* to the two editions of the book, [2] and [3].

Due to the idiosyncracies of writing style, the modern reader can be forgiven for completely missing the key messages that Thompson tried to get across. Here, I will attempt to tease them out. I shall also try to relate them to historical trends in theoretical biology, particularly in the field of developmental biology, in the more than 100 years since OGF was first published. In most instances, in line with P.B.Medawar's critique of OGF [9], in which he states that the sustained influence of OGF has been 'intangible and indirect', we may feel that the apparent links with modern developments are quite possibly accidental, but they can always be interpreted as being at least strikingly prescient.

In Section 1.3 below we discuss twelve key messages, largely philosophical in spirit, the twelfth of which is by far the most speculative, and embodies one of Thompson's more prescient insights :

1.3 Thompson's Key Messages from 'On Growth and Form'

I. The need for a change of mind set This is addressed to the 'zoologist or morphologist [who] has been slow, where the physiologist has been long eager, to invoke the aid of the physical or mathematical sciences'. Thompson identifies the availability of numerous theories within the traditional confines of biology, which 'though a little lacking in precision', have provided their own routes towards new lines of thinking, and the elaboration and testing of hypotheses, without the need (apparently) for an appeal to the greater precision offered by mathematical and physical theories and methods. In particular, he cites taxonomy - the 'art of classification' - as 'an endless search after the blood relationships of things living and the pedigrees of things dead and gone'. Confinement to such theories and disciplines, stems from 'a reluctance to compare the living with the [inanimate]' - ***see also message VII below*** - or 'to explain by geometry or by mechanics the things which have their part in the mystery of life'. This in turn tended to inhibit amongst biologists any move towards applying mathematical and physical techniques and ways of thinking (OGF(1), pp 2-3).

II. Beware the limitations of the teleological concept Teleology attempts to explain origins through the concept of *Final Cause* in terms of *End, Purpose or Design.*

The centrality of this concept to the naturalist's thinking about phenomena such as *fitness* and *adaptation* - e.g birds evolved feathers in order to fly - was itself a deterrent to seeking for physico-mathematical descriptions of evolution.

Aristotle was a teleologist, and is well known for his belief that 'In the works of Nature, *purpose*, and not *accident*, is the main thing' (OGF(1) footnote, p4). This argument for the centrality of the *final cause* had, by 1917, carried through to embryology. Early processes of growth and development were thought of as *prospective*, and embryonic phenomena were interpreted in terms of their purpose in generating the body of the adult organism. This complied with Aristotle's belief that the organism is the *telos* - the *final cause* - of its own processes of growth and morphogenesis.

But mathematical concepts like space and number were seen by Aristotle to be independent of any mechanisms of *causation* - so as a teleologist he understood mathematics to stand apart from any problems of causation. This is embodied in Aristotle's parable: 'The house is there that men may live in it; but it is also there because the builders have laid one stone upon another', (OGF(1), p5). It is the neglect of the latter class of cause in biology (termed by Leibniz the *efficient cause* - more likely termed the *physical cause* nowadays) to which Thompson wished to draw attention.

Even with the advent of Darwin's Theory of Natural Selection, teleology found a reformulation which has enabled it to continue its utlility to the present day, and thus to continue to offer a barrier to the adoption of mathematical and physical approaches to the study of fitness and adaptation. Thompson remarked in connection with the process of *natural selection*, that in attaining adaptations such as form and colour which fit the organism for survival, we reach an 'adaptation without design, a teleology in which the final cause becomes little more, if anything, than the mere expression or resultant of a sifting out of the good from the bad, ..., in short a process of mechanism'. He cites Janet (in *Les Causes Finales* (1876), p350 [10]) who observed - in Thompson's own translation - that the 'apparent manifestations of purpose or adaptation [thus] become part of a mechanical philosophy', (OGF(1), pp4 - 5). In effect, we reach a teleology without a *telos.*

(***How this relates, more specifically, to the Darwinian perspective is discussed further in 2.1.2 below, under the banner of 'functionalism', showing also how the concept of 'function' in biology leads in turn to ideas of design, purpose, and teleology.***)

III. Explaining development other than through teleology Thompson put it this way: 'But the use of the teleological principle is but one way, not the whole or the only way, by which we may seek to learn how things came to be, and to take their places in the harmonious complexity of the world', (OGF(1), p5). In OGF(2), he goes on (p6), to credit Democritus as being the 'first of the physicists', who 'chose to refer all natural phenomena to *mechanism* [Thompson's own emphasis] and to set the final cause aside'. Thompson characterises this approach as the search for *causes* in the 'unchanging laws of matter and energy'. Instead of *ends* the physicist seeks *relations* between phenomena A and B: e.g. such as *antecedence* (in which A is an essential prerequisite in time for the occurrence of B); or, *inseparable concomitance* (in which A and B necessarily occur together, or in some quantitative relation to one another, such as proportionality). In this view, phenomena are considered *mechanistically* (by analogy with some *mechanical construct*, real or theoretical).

(***For more on analogy see messages VI and VII below.***)

IV. The need to unify mechanistic and teleological principles Thompson asserts that after positing a final cause for a given phenomenon, we should perhaps undertake the more difficult task of explaining it 'on the plainest principles of mechanical causation', and furthermore, 'it may be useful and appropriate to see how the final cause would tally with the other, and lead towards the same conclusion', (OGF(2), p7). The risk has always been that the teleological interpretation has often inhibited the pursuit of the more rigorous enquiry demanded for an understanding of mechanical causation (*efficient causes*). He cites (OGF(1), pp5-6) the 13th Century philosopher Roger Bacon as follows: '[a leaning towards the side of the final cause] hath intercepted the severe and diligent enquiry of all real and physical causes.' [11]

Thompson believed that we must favour neither the final nor the efficient cause, 'for their union is rooted in the very nature of totality'; and further, 'In our own day the philosopher neither minimises, nor unduly magnifies the mechanical aspect of the Cosmos; nor need the naturalist either exaggerate or belittle the mechanical phenomena which are profoundly associated with Life, and inseparable from our understanding of Growth and Form', (OGF(2), p7).

V. Difficulties surrounding ultimate, or real causation The above fusion of concepts of final and efficient causes was very much a concern of Isaac Newton, and Roger Bacon before him, and essentially confronts the apparently insurmountable problem of giving, to quote Thompson's own words, any credible 'account of the relation of cause and effect from the empirical point of view', (OGF(2), p8). He reassures us, by claiming this need not hinder us 'in our physical enquiry. As students of mathematical and [experimental] physics we are content to deal with those antecedents, or concomitants, of our phenomena without which the phenomenon does not occur. ... Our purpose is still adequately fulfilled: inasmuch as we are still enabled to correlate, and to equate, our particular phenomena with more and ever more of the physical phenomena around', (OGF(1), p6).

This presages a significant aspect of modern approaches in the study of *complex phenomena* (such as *developmental systems* and *processes*). He continues with a passage which may evoke very current-sounding ideas to the modern reader: '[and so we must] weave a web of connection and interdependence which shall serve our turn, though the metaphysician withhold from that interdependence the title of causality', (OGF(1), p6). We can interpret this nowadays in terms of the thriving disciplines of *general system theory*, or the *theory of complex networks*.

(***Covered in more detail in Chapters 4 and 6 respectively.***)

This in turn highlights a feature of Thompson's vision, implementation of which could not effectively be pursued in his time, as this would await technological developments, in particular powerful and fast digital computers; development of conceptual constructs such as general system theory and cybernetics; mathematical developments not even conceived of in 1917 (nor barely so in 1942) such as *graph* and *network theories*; and the empirical knowledge of developmental processes and genetics not yet acquired in Thompson's time.

VI. To recognise the power of analogy The search for physical causes and interdependencies, as described above, can fruitfully be complemented by another explanatory principle developed by Aristotle - ' the search for relations between things apparently disconnected, and for "similitude in things to common view unlike" ' - as quoted by Thompson from Kepler (OGF(2), footnote in Latin, p9). The power of analogy can be misrepresented, or underestimated. Many of the examples of analogy Thompson uses in his book, though intriguing in themselves, are of limited value in explanations of the development of form in living organisms, even the hard-shelled, single-celled foraminifera which he studied in detail. The comparisons in forms of Roman pottery with various species of *Lagena* (illustrated on pp414-5 of OGF(2)) are unconvincing. (Figs 1.3.1a and 1.3.1b.) However, as Thompson points out, there is more to analogy than this - 'Newton did not shew the cause of the apple falling, but

(a) Fig.130 of OGF(2), 'Various species of *Lagena*. After Brady'

(b) Fig.131 of OGF(2), 'Roman pottery'

Figure 1.3.1: From OGF(2), pp414-5, Comparing Forms of Various Species of *Lagena*, with Roman Pottery

he shewed a similitude between the apple and the stars.' (OGF(1), p6). In OGF(2), p9, he continues '... By doing so he turned old facts into new knowledge; and was well content if he could bring diverse phenomena under "two or three Principles of Motion" even though the "Causes of these Principles were not yet discovered" [the "double-quotes" are Thompson's own]'. Philosophers as eminent as David Hume and J.S.Mill are cited in OGF as believing that all reasoning whatsoever depends on resemblance and analogy, and the power to recognise it. (OGF(2) footnote, p9).

VII. Essential similitudes between living and non-living matter Thompson argued that traditionally, investigations were more focused on the 'differences and fundamental contrasts' between the phenomena exhibited by organic (or animate) as opposed to inorganic (inanimate) matter, at the expense of seeking 'principles or essential similitudes' demonstrating the commonalities relating them.

Physicists had long sought unification of the laws of nature as far as non-living systems are concerned, and in so doing approached the 'riddles of form' in such contexts as 'waves of the sea, the ... ripples on the shore, ..., the outline of the hills, the shape of the clouds', and many more. (OGF(1), p7). Thompson saw these as 'so many problems of morphology, ... solving them by reference to their antecedent phenomena, in the material system of *mechanical forces* to which they belong, and to which we interpret them as being due'.

He urged that things are not otherwise for living things, and that the same (and possibly some other as yet undiscovered) *unifying principles* should apply in the living as in the non-living worlds. 'Cell and tissue, shell and bone, leaf and flower, are so many portions of matter, and it is in obedience to the laws of physics that their particles have been moved, moulded and conformed'. (OGF(1), p7).

VIII. Problems of form and growth are essentially physical problems Thompson claimed that, though problems of *form* may at the outset be considered as problems in mathematics, introducing the problem of *growth* to the processes of origin and development of form becomes essentially a physical problem, and so 'the morphologist is *ipso facto* a student of physical science'. (OGF(1), p8). In relation to growth, and the development of a more (or less) complicated structure, Thompson underlines the above message as follows (paraphrasing from OGF(1), p11): 'when we abstract our thoughts from the material to its form ... , then *force* [is to be perceived] as the [underlying] cause by which these *forms* and *changes of form* are brought about.'

It is this aspect of Thompson's programme that confronted the issue of whether there was still a need (in 1917 more than 1942) of *vital forces*, as postulated in the *vitalist* philosophy, to fully explain the phenomena of life. Thus, given the date of first publication, there can be discerned a hint of vitalism in his thinking. Regarding the attributes of life, he says 'One does not come by studying living things for a lifetime to suppose that physics and chemistry can account for them all' (OGF(2), p14) , and 'We want to see how, in some cases at least, the *forms* of living things, and of their *parts*, ..., can be explained by physical considerations, and to realise that in general no organic forms exist save such as are in conformity with ordinary physical [and mathematical] laws'. (OGF(1), p10; he added the 'and mathematical' in OGF(2), p15). Thus, although he did not totally rule out the possibility of vital forces, he saw the essential need for life phenomena to be understood in terms of physics and mathematics.

IX. Moving from physico-chemical to physico-mathematical principles Thompson promoted strongly the need to complement the burgeoning growth of knowledge in the physics and chemistry underlying the functioning of living organisms, by giving greater emphasis to the more physico-mathematical (or *dynamical*) investigation of these functions, in morphology and morphogenesis in particular.

This message was largely ignored in the decades following OGF(1) in 1917, and was not taken up seriously in developmental biology until the 1980s. Of course, most of the significant progress in biology during that period was in our understanding of biochemistry and molecular biology, linked to the discovery of the role of DNA as the conveyor of genetic information. Arguably, if Thompson had chosen this route to elaborate his ideas, most of his deliberations would long have been forgotten. However, his focus was on *growth and form* rather than *function* (more the realm of the physiologist), and this left the door open for physico-mathematical investigations, as advocated by him. Since the 1980s the need to combine chemical and genetic knowledge, with the role of physical phenomena in growth and development has come to motivate more and more the work of empirical and experimental, as well as theoretical, researchers.

Thompson realised, and expresses throughout his book, that the contemporary limitations on mathematical and empirical knowledge (not just his own) would inhibit progress in responding to his proposed programme of research. 'It is but the slightest adumbration of a dynamical morphology that we can hope to have, until the physicist and the mathematician shall have made these problems of ours their own ... .' (OGF(1), p8). Of course, it is the dynamical aspect of developmental systems that is currently occupying much attention among both experimentalists and theoreticians. Constructs such as *dynamical systems theory* (more popularly known as *complexity theory*), and its mathematical underpinnings (*nonlinear systems theory* or *nonlinear dynamics*) have emerged into prominence in the last 30 years. They offer some routes by which the problems posed by Thompson have been (and are being) addressed, relying (of course) on the availability of modern high speed computation.

(***This aspect is considered further in Chapters 6 and 7.***)

X. The significance of the term *force* as used by Thompson His concept of force was precisely that of Newtonian mechanics in elementary physics: a force is recognised by its action in changing or preventing a change in motion, and/or acceleration/deceleration along the path travelled by the body on which the force acts.

A great difficulty for Thompson was that there can be no clear definition of rate of growth in an organism, or part thereof, which would enable straightforward application of Newtonian mechanics to problems of organismic growth. As he himself said, 'And while growth is a somewhat vague word for a very complex matter, which may depend on various things, from simple imbibition of water to the complicated results of chemistry of nutrition, it deserves to be studied in relation to form, whether it proceed by simple increase of size without obvious alteration of form, or whether it so proceed as to bring about a gradual change of form and the slow development of a more complicated structure.' (OGF(1), pp10-11).

The following statement (OGF(1), p11), ***ties in well with Thompson's message***

XI below, interpreting the shape of an organic structure in terms of a 'diagram of forces': 'The form, ..., of any portion of matter, whether it be living or dead, and the changes of form that are apparent in its movements and in its growth, may in all cases alike be described as due to the action of a force.'

Elaborating on this, he then claims further that 'In short, the form of an object is a "diagram of forces" [Thompson's own "double-quotes"], in this sense, at least, that from it we can judge of or deduce the forces that are acting or have acted upon it'; and '... the state, including the shape or form, of a portion of matter, is the resultant of a number of forces, which represent or symbolise the manifestations of various forms of energy', (OGF(1), pp11-12).

(***In message XI below, we will explore further what Thompson meant by this. In section 1.4, and in Chapters 2 and 3 below, we will evoke some of the related hypotheses he or his contemporaries proposed, which were reasonable in 1917, given the state of empirical knowledge and the limitations on available technology prevailing at that time.***)

It is perhaps such 'reasonable hypotheses' which were among the biggest contributions the book made to biology at the time, for they stimulated research ideas, in some quarters at least, more often than not spawning results that contradicted Thompson's postulates. Such negative results were nonetheless of much significance to progress in understanding.

Where he could, Thompson would declare a caveat in those cases of 'known unknowns' that were emerging at the time. For instance, '... [for a simple organism such as *Amoeba*] ... if our short list of its physical properties and conditions be helpful to our further discussion, we need not consider how far it be complete or adequate from the wider physical view.' He exemplifies this in a footnote stating, 'With the special and important properties of *colloidal* matter we are, for the time being, not concerned.' (OGF(1) footnote, p12; the above *italic* emphasis is Thompson's own.) Inevitably, at that time Thompson had an oversimplified view of the cell surface, treating the cell as analogous to a simple fluid droplet, *ergo* 'Like other fluid bodies, its surface, ... is the seat of molecular force exhibiting itself as a *surface tension*, from the action of which many important consequences follow, which greatly affect the form of the fluid surface.' (OGF(1), p13).

Of course, Thompson could know nothing of the complexities of the cell

surface membrane, nor of the manifold cell surface properties that embedded glycolipid and glycoprotein molecules could determine. (e.g. by mediating forces of adhesion, or even repulsion, between cells, which may be switched on or off by genetic control mechanisms.) None of the requisite theoretical and empirical knowledge could be accessible in Thompson's era, constituting from his perspective 'unknown unknowns' which he could not even declare as caveats. This is just one instance of how the advances in molecular biology, and cell cytology at the nanoscale, have made many of Thompson's hypotheses overly simplistic and obsolete, though reasonable at the time.

XI. The significance of the term *form* as used by Thompson The findings of much subsequent empirical work in the inter-war years (1918-1939) underlined the futility of any attempt to find some *growth-controlling principle* in this context (e.g. P. Weiss, *Chemistry and Physiology of Growth* (1949) [12]). C.H.Waddington, after discussing the range of processes involved in growth (and *degrowth*) prevailing among developing organisms, stated 'it is hardly to be expected that any very simple formula can fit all cases' [13], p285. Hence, the overall growth concept proved difficult to quantify in any meaningful way (with or without the application of Newton's laws, and his concept of force) and so attention soon switched to development of *form*, and in particular to the *relative growth of parts*, which Thompson saw as a key element in the development or evolution of form. This has acquired the name *allometry* in modern usage. (In the relatively few references to this concept made in OGF, Thompson uses Julian Huxley's term *heterogony*, (OGF(2), pp205 - 213; and also p279 where the role of heterogony is related to phenomena of regeneration after injury). Essentially this defines, for some linear measure, the magnitude $\boldsymbol{x}$ of the whole organism as a function of a correspondingly defined measure $\boldsymbol{y}$ of some part of the organism. Many real examples were reported, showing how the growth rates of parts (with respect to time $\boldsymbol{t}$) within some more complex body structure, relative to that of some standard part, vary in a graded manner between locations within the structure. Hence this was an essentially descriptive treatment of growth and developmental processes, making no references to possible causes (involving forces or not).

Thompson's Theory of Transformations, the subject of Chapter XVII of OGF, in particular regarding the transformation of forms in the ontogenetic context, has a bearing here. It is perhaps the best-known part of the book, and it concerns (mainly) how the differences between the forms of related species can be represented geometrically, using transformations of systems of Cartesian coordinates. Thompson termed this the *method of coordinates*. One of the forms is chosen as the *Cartesian* *type* and is represented on a 2-dimensional Cartesian system of orthogonal coordinate axes. Any form into which the Cartesian type is to be transformed is then generated by an appropriate transformation of the orthogonal system of axes for $\boldsymbol{x}$ and $\boldsymbol{y}$ - e.g. by altering the relative directions of the axes; by changing the ratio of $\boldsymbol{x/y}$; or by substituting for $\boldsymbol{x}$ and/or $\boldsymbol{y}$ some function of either or both these variables. Thus, a new system of coordinates is obtained, the deformation of which will be precisely followed by deformation of the original (Cartesian) type, into a new form.

Though this is interesting in a purely descriptive sense, Thompson admits that there is little attempt at causal explanations for the transformations represented. Indeed, a given transformation might well be interpreted as a transition from one species into another by a phylogenetic (evolutionary) process, or (as in a relatively few of the examples Thompson uses in OGF) as an ontogenetic (developmental) process changing one embryonic stage into another.

Thompson seems not unduly worried by such a disconnect between his mathematics and the real world of observation, experiment and causation. This was at the root of many of the criticisms he received - particulary after the publication of OGF(2). (e.g. see subsection 3.3.1, pp50-52, where some of the reviewers' remarks are quoted.) Along with the absence of genetics, Thompson was much criticised for his so-called *Platonism*, which put Plato's *idealism* on a higher plane of discourse than *empiricism.* On OGF(2), p1094 (in the conlusion to his final chapter) he aligns himself with the teachings of Plato and Pythagoras, with the claim that 'In natural history, "Cuvier's types" [Thompson's own "double-quote" marks]', which are Plato's *ideals* under another name, 'may not be perfectly chosen nor numerous enough, but types they are; and to seek for stepping stones across the gaps is to seek in vain, forever.'

Indeed, Thompson saw a disconnect not only between the Platonic viewpoint and empiricism, but also with mathematics itself. e.g. he cites, in an extended footnote, pp722-3 of OGF(1), the '*obiter dictum*' of his very empirically-based contemporary, T.H.Huxley: 'Mathematics is that study which knows nothing of observation, nothing of experiment, nothing of induction, nothing of causation'. (From Florian Cajori, *A History of Elementary Mathematics* (1896) [14].) [1]

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[1] T.H.Huxley, grandfather of J.S.Huxley (whom I also cite here) was an accomplished comparative anatomist, best known for his advocacy of Darwin's theory of evolution, and hence for his own (self-styled) claim to be 'Darwin's bulldog'. But unlike Darwin, he was very much an empiricist, and would only trust what he could experience with his own senses. He also had a very influential role in promoting scientific education, which probably accounts for his mention in Cajori's book, which has the subtitle 'Hints and

However, relating the above procedure to his postulated involvement of forces in the developmental process, Thompson does claim (OGF(1), p720, and also, in an updated and expanded context, (OGF(2) p1027) that, '... in the representation of form and in the comparison of kindred forms, we see in the one case a *diagram of forces in equilibrium* ... , in the other ... the *magnitude and direction of the forces* which have sufficed to convert the one form into the other'.

(***More specific examples of allometry, and of the transformation of forms, will be considered in Chapters 2 and 3, where we consider further some descriptive approaches to modelling growth and development.***)

XII. Thompson's key, most prescient, message Our final, more speculative, message from Thompson, to which we will make (at least) implicit reference throughout the following Chapters, relates (OGF(1), pp12-14) to 'less well understood' *forces* which are 'peculiar to living things' ***- see also message VIII above***. On the face of it, we could be forgiven for detecting a hint of vitalism still in his fondness for making such statements. However, he faced the problem that the conceptual vocabulary was not available to him to speak of causal agents other than *force* and the *'operations of energy'*. Yet he had an insight (OGF(1), p14; and also, in a wider context, OGF(2), pp19-20) that cried out for the broader vocabulary available today (the *italics* in the following quote are Thompson's own): '... in dealing with the facts of embryology or the phenomena of inheritance, the common language of the books seems to deal too much with the *material* elements concerned, as the causes of development, of variation, or of hereditary transmission.' He was not in a position to suggest what exactly the *non-material* elements might be, for he knew nothing of the role of genes as regulatory agents, and not just as structural determinants; of Information Theory and the role of information transmission (perhaps the closest theoretical constructs available at that time, related to thermodynamics and entropy - for the dominant technology of the time was, of course, that of steam power); nor of Systems Theoretic and Cybernetic ideas, such as control systems, regulation and feedback. More latterly, a vast body of knowledge has emerged, around nonlinear mathematics and complex systems; along with the related finite state mathematics, spawning Graph and Network Theories, which feature so strongly nowadays in the study of *gene regulatory networks*.

Thompson was therefore prescient in warning: 'We may readily admit then, that besides phenomena which are obviously physical in their nature, there are actions visible as well as invisible taking place within living cells which our knowledge does not permit us to ascribe with certainty to any known physical force: and it may

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or may not be that these phenomena will yield in time to the methods of physical investigation'. (OGF(1), p14, and OGF(2), p19).

He was proved correct in this assertion in the 100 years post-1917. If we were to translate his statement into language better reflecting our present day understanding of Developmental Biology, who knows, he may well be proved equally correct in the next 100 years. Message XII has a significant corollary, which we discuss in 2.2, p34 below.

1.4 Some Physico-mathematical Principles Highlighted by Thompson in 'On Growth and Form'

Thompson's key message IX, sketched above, spells out in general and philosophical terms the need to complement the rapidly expanding knowledge of biochemical and physical processes underlying the functioning of living organisms, with the realisation that there are overarching physical and mathematical principles governing developmental biology in particular. Implicitly, some features of developmental processes are best understood in terms of general law, and in the language of biophysics, rather than through the in-depth (and frequently unfathomable) descriptions of biochemical processes dominating the thinking of developmental biologists in the 20th Century.

In messages X and XI above, two sets of such principles, concerning the significance of force and form, and their interaction in the shaping of organic structures were introduced (and will be elaborated further in 1.4.1 below, and in the Chapters to follow). Four other classes of physico-mathematical principles, featured by Thompson in OGF, concerned: the effects of scale on biological systems; the roles of conservation and minimisation principles operating in various contexts; the roles of symmetry and symmetry-breaking; and (although featured less strongly) the laws and concepts of thermodynamics.

(***Let us consider all these briefly below. They will also feature, explicitly or implicitly, throughout the chapters to follow.***)

1.4.1 Force as an Explanatory Principle in the Determination of Form

The main principle Thompson applies in attempting to explain form, or changes of form is that of *force*, ***as discussed in message X above***. This is summed up in Thompson's statement, in OGF(1), p11: '... when we abstract our thoughts from the material to its form, or from the thing moved to its motions, when we deal with the subjective conceptions of form, or movement, or movements that change of form implies, then Force is the appropriate term for our conception of the causes by which these forms and changes of form are brought about'.

Elaborating on his idea of 'force' here, Thompson brings in the other physical phenomena he needs in order to approach the problem of development : 'In an organism, ... it is not merely the nature of the *motions* of the living substance which we must interpret in terms of force [as described in kinetics], but also the *conformation* of the organism itself, whose permanence and equilibrium is explained by the interaction or balance of forces, as described in statics' (OGF(1), pp11-12). (The *italics* here are Thompson's own.)

Thompson also gives an indication of the principal forces, and properties of matter, with which we need to deal: many of these are familiar and well understood, e.g. *cohesion, friction, gravity, pressure from outside the cell, intermolecular forces, surface tension.* However, the existence and complex nature of the cell membrane had not been established, even in 1942, when the revised edition - OGF(2) [3] - was published. This, and many other aspects of cellular ultrastructure, would eventually make many of Thompson's rather naive suppositions about how these basic examples of 'force' might actually act within living systems, come to appear as extreme oversimplifications.

(***See also the comments pertinent to this, under messages X, XI and XII, pp10-16 above; and in relation to growth of bone in particular, in Chapter 3, subsections 3.1.1 and 3.1.2.***)

When it comes to the (at the time) less well understood 'forces' which Thompson characterises as 'peculiar to living things', he uses terms such as *chemical, electrical, and thermal influences within the cell, growth as a force arising from chemical and electrical activity, attractions and repulsions within the cell nucleus, driving the 'caryokinetic figures' of chromosomal movement*, OGF(1), pp12-14. In admitting such uncertainties, Thompson stated, ' ... [maybe such as yet to be explained] phenomena will yield in time to physical investigation. [Yet] ... we have no clear rule or guide as to what is 'vital', and what is not [Thompson's own quote marks]; the whole assemblage of ... *vital phenomena* or *properties* of the organism, cannot be classified into those [of] physical origin, and those that are ... peculiar to living things' (OGF(1), p14).

1.4.2 The Principle of Similitude, and the Effects of Scale

Thompson presents, in his important Chapter II *On Magnitude*, observations on the significance of scale and its effects on the growth, functioning and form of organisms which exist at different scales of magnitude. The mathematics of proportionality (a quantitative aspect of similitude) features strongly throughout this Chapter, with its key argument that surface/volume ratio declines with increase in spatial dimensions.

As he states, OGF(1), p17, '.. a much deeper interest arises out of this changing ratio of dimensions when we come to consider the inevitable changes of physical relations with which it is bound up'. He links this to his other central tenet that growth and form are subject to forces, internal and external to the organism, and that ensembles of qualitatively and quantitatively different forces apply in environments operating on different scales. He continues on p17: '... for scale has a very marked effect upon physical phenomena, and the effect of *scale* [Thompson's *italics*] constitutes what is known as the *principle of similitude*, or of *dynamical similarity* [my *italics*]'. This principle was first drawn up by Galileo with a 'great wealth of illustration, drawn from structures both living and dead.' (See extensive citations in OGF(1), pp18-20, including some from Herbert Spencer, e.g. [15], who applied 'elementary engineering experience' in the use of the principle of similitude in biology.)

Much of the Chapter is given over to the analysis of the proportionalities involved in various forms of locomotion, including swimming, flight, and walking. He sums this up by stating (OGF(1), pp31-32) that 'the general result, attained under very different conditions and arrived at by very different modes of reasoning, is in every case that the velocity tends to vary as the square root of the linear dimensions of the organism.' Thompson also recognises an important distinction, both quantitatively and qualitatively, between three classes of forces: the *gravitational*; forces *internal* to the organism; and *environmental forces.*

In OGF(2), Chapter 2 has more scope than in OGF(1), spanning 56 as opposed to only 34 pages. It is better organised, and comes to coherent concluding remarks, which are absent from this chapter in OGF(1). For instance, on p77 he is able to reach conclusions, and language, more in line with present-day thinking and terminology. 'We found, to begin with, that "scale" [Thompson's own "double-quotes"] had a marked effect on physical phenomena, and that increase or diminution in magnitude might mean a complete change of *statical* or *dynamical equilibrium.* In the end we begin to see that there are *discontinuities* in the scale, defining *phases* in which different forces predominate and different conditions prevail'. With regard to living things in particular, he sees a range of magnitudes 'wide enough to include three such *discrepant conditions*' :

- Gravitation rules on the human scale, determined by the mass, density and size, and on the form, structure and composition, of planet Earth;

- The forms of smaller organisms can, in effect, be largely or wholly independent of gravity, and 'largely if not mainly due to the force of surface tension [OGF(1) p33]'. And, on OGF(1) p34, he goes on to say ' ... we have reached an order of magnitude in which *intermolecular forces* [can outweigh] the force of gravity, and also those other forces leading to movements of convection which are the prevailing factors in [larger material aggregates]';

- In OGF(2) he includes '... a third world, where the bacillus lives, [in which] gravitation is forgotten, and the *viscosity* of the liquid, the resistance defined by Stokes's law, the molecular shocks of the Brownian movement, doubtless also the electric charges of the ionised medium, make up the physical environment [and thus come to predominate]'.

Summing all this up (OGF(2), p77) he comments, 'The predominant factors are no longer those of scale; we have come to the edge of a world of which we have no experience, and where all our preconceptions must be recast.' Though Thompson's Chapter II of OGF remains among the most complete discussions of the effects of scale on morphogenesis, some more recent examples worthy of note include those of J.T.Bonner (1952) *Morphogenesis* [16]; and T.A.McMahon *et al* (1983) [17].

(***Subsections, 1.4.3 to 1.4.5 below, hint at the forms of 'recasting' Thompson might have had in mind here.***)

1.4.3 Conservation and Minimisation Principles

Thompson advocated that the laws of physics should - sometimes most efficiently, and also more intuitively - be expressed, not in terms of governing equations, but in terms of quantities that must be minimised. (Further discussion, B.H.Bonney *et al* (2018) [18], submitted for review and publication.) In fact, this idea is one of the great organising themes of OGF, and one to which Thompson returns repeatedly - for example in his treatment of honeycombs (OGF(1), pp327-334; and much elaborated in OGF(2), pp525-544). His point was that biological forms derive their structure in large part from the action of physical *conservation and minimum principles*, and similarity in form is, at least partly, due to similarity in underlying conservation principles.

Thompson's theory of transformations, ***outlined under key message XI above***, is one of the more interesting areas in which he attempts to demonstrate the role of conservation principles. In comparing the shapes of related organisms, he asserts that the morphologies of related species can be thought of as mathematically distorted versions of one another, and he argues that similar biological shapes must represent some basic conservation in the physico-chemical developmental process resulting in deformed but still recognisable resemblances in the resulting biological patterns.

(***We return to this topic in Chapters 2 and 3, along with some critique of Thompson's 'method of coordinates', and its utility in modelling both ontogenetic or phylogenetic changes in form.***)

Of course, many modern theories in mathematical physics are formulated in terms of minimum principles, which lead not only to equations for various mechanical phenomena, but also to geometrical intuitions about the nature of those solutions, also including the existence of conserved quantities. Thompson himself was well aware of the historical origins of these modern trends in physics, explaining for instance the development of the concepts of Kinetic and Potential Energy (K.E and P.E.) from the time of K.S.Gauss (1830), and P.G.Tait (1866 and 1868) [see OGF(1), pp33-35 and 207-209]. For example, regarding theories of capillarity and of surface energy in droplets of liquid, Thompson explains eloquently (OGF(1), p208, ' ... and we know, as a fundamental theorem of dynamics, as well as of molecular physics, that the P.E. of the system *tends to a minimum*, and finds in that minimum its *stable equilibrium*'. Relating this to the form of a cell, he goes on to state, '... the *energy equations of the surface of a cell, or of the free surfaces of cells in partial contact, or of the partition surfaces of cells in contact with one another*, all indicate a *minimum of [P.E.] in the system*, by which *minimal condition* the system is bought about, *ipso facto*, into *equilibrium*'. In OGF(2) p356, he relates these ideas to chemical equilibria: 'Two chemical substances in reaction so behave that their *thermodynamic potential* tends to a minimum'.

In both editions, Thompson's Chapter V *On the Forms of Cells* gives some sound physical theory around *minimal principles*, in such contexts as *surface tension and surface energy*; *minimal areas in water droplets*; *least surface for a given volume and the principle of minimum areas*; and *the principle of least action.* In OGF(2), footnote to p356, he credits Lagrange (1788) [19], 'following Euler's lead', as the first to present the latter principle as a general result from the laws of mechanics, rather than just some 'metaphysical principle'. But by way of caution, Thompson rightly echoes his key philosophical ***message V above***, by observing (OGF(2), p356) 'The principle of least action *explains nothing*, it tells us nothing of *causation*, yet it *illuminates a host of things*'.

Between the two editions, Thompson, who in the view of his biographers had no command of calculus, nor much trust in differential equations, had come to appreciate their importance - e.g. in OGF(2), p356 he states: '... the natural philosophers of the 18th Century were engrossed in minimal problems; and the differential equations which solve them nowadays are among the most useful and most characteristic equations in mathematical physics.'

1.4.4 Symmetry and Symmetry-breaking

Thompson's use of the term '*symmetry*' is that deriving formally from, for instance, the external form of a crystal, which in turn derives from the *regularity* apparent in the internal lattices in which the component atoms or molecules are arranged. As he puts it, OGF(1), p209: 'Complex and obscure as the attractions, rotations, vibrations, [etc], within the crystal may be, we rest assured that the configuration, repeated again and again, of the component atoms is *precisely that for which the energy is a minimum*; and we recognise that *this minimal distribution is of itself tantamount to symmetry and stability*'.

He quotes, OGF(1), p209, Ernst Mach's explanation (1902) [20] of what *physical equilibrium* has to do with *formal symmetry* and *structural regularity* : 'In every symmetrical system every deformation that tends to destroy the symmetry is complemented by an *equal and opposite deformation* that *tends to restore* it. In each deformation, *positive and negative work* is done. One condition, therefore, though not an absolutely sufficient one, that a maximum or minimum of work corresponds to the form of equilibrium, is thus supplied by symmetry. Regularity is *successive symmetry*; there is no reason, therefore, to be astonished that the forms of equilibrium are often symmetrical and regular'. In OGF(2), footnotes to pp356-7, Thompson cites an expanded list of relevant material, some (but not all) of which was published after OGF(1) : - the mathematical treatment by Jacob Steiner (1836) [21]; and on the biological side, works of F.M.Jaeger (1917) [22]; and F.T.Lewis (1923) [23].

Using this definition of symmetry, Thompson's approach is often at odds with many experimental biologists who study 'symmetry' and its underlying molecular mechanisms, in the sense of such anatomical definitions as *radial symmetry* (e.g. as in starfish), or *bilateral symmetry* (as in any animal form with an anterior (head) and posterior (tail) end, thus defining an *antero-posterior* axis of development). Thompson's approach restricts its applicability, in their view, to simpler forms of ontogeny, involving single cell structures, or arrangements of cells in films or tissues, which many would see as self-assembly, or self-organisation, rather than genuine embryogenesis.

(***e.g. see Chapter 3, subsection 3.3.3 below; and C.H.Waddington's comments in Chapter XX of [13], which give a good synopsis of the limitations of Thompson's approach***.)

This latter point helps explain why Thompson never considered the role of *symmetry-breaking* in embryogenesis, because the systems he found of interest were in the main too simple. However, his Theory of Transformations (***key message XI above***) did concern changes of form in more complicated organisms, with anatomical symmetries familiar to biologists, but could not lead to symmetry-breaking, as Thompson's ideas concerned intuitive geometrical changes involving only small step changes, and did not allow for the *bifurcations* which feature in modern topological modelling (***see Chapters 6 and 7***).

1.4.5 The Second Law of Thermodynamics - evolution and entropy as analogues

On OGF(2), p358, Thompson, having linked minimisation principles to symmetry, goes on to explain the link with Thermodynamics : 'Moreover, the *principle of least action* [***see above***] is but a setting of a still more universal law - that the world and all its parts thereof tend ever to pass from less to more probable configurations; in which the physicist recognises the *principle of Clausius*, or Second Law of Thermodynamics, and with which the biologist must somehow reconcile the whole "Theory of Evolution" ["double-quotes" here are Thompson's own]'.

However, in common with some earlier of Thompson's messages stated above, he was most concerned here with the significance of analogy: 'Organic evolution has its physical analogue [in the universal law of thermodynamics]'. He points out that it has been described (e.g. in Lotka's *Elements of Physical Biology* (1925) [24]), as 'the law of evolution of the world ... and we call it , after Clausius, the principle of *entropy* which is a literal translation of *evolution* into Greek' (OGF(2), p11). Though there may well be a valid physical interpretation of this analogy in terms of our modern understanding of both entropy and evolution, it would seem that this is more a case of a classicist/scientist allowing etymology to dominate too much in the recognition of analogy. (There is no mention at all in OGF(1) of Clausius, nor of thermodynamics, nor entropy, nor of the Second Law itself.)[2]

In Chapter 6, we will consider further the significance of the Second Law in our understanding of the origins of spontaneous order from chaos, as encountered in organismic development.

Even now, there are so many unanswered questions to be addressed, both in theoretical biology, and in the related empirical and experimental sciences. Thompson's general principles, both those which are philosophically grounded, and those derived from physics (as opposed to the biochemistry, molecular biology, and laws of genetics and natural selection which still dominate biological

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[2] In OGF(2), the term 'entropy' appears in the index as 'entrophy' - a word that does not to my knowledge occur in the scientific lexicon, though it could plausibly be coined in the study of growth and nutrition. From the context of OGF(2) p11, clearly 'entropy' was intended!

thinking today) remain potentially as guiding lights, at all times available in approaching such questions. Let us bear this constantly in mind in the Chapters to follow, as we survey the progress made in developmental biology since Thompson's era.

CHAPTER 2

Descriptive Mathematical Biology

In the 1917 First Edition of his book, OGF(1) [2], p10, D.W.Thompson declares that his 'sole purpose is to correlate with mathematical statement and physical law certain of the simpler outward phenomena of *organic growth* and *structure* or *form*, while ... regarding the fabric of the organism, ..., as a material and mechanical configuration'.

However, his focus on growth, structure and form here, leads him to ideas which have a strongly *descriptive* element to them, but which do not establish, or employ, much in the way of *explanatory principles*. Therefore, they make little contribution to our understanding of the mechanisms by which the forms described come about.

Yet there are other instances in his writing where Thompson strongly advocates *explanatory principles*, usually based on elementary principles of physics, especially mechanics. The divide in Thompson's mind between explanatory principles, and pure description appears to arise between explanation of growth and morphogenesis in small (often unicellular) microrganisms, or simple multicellular or unicellular structures on the one hand; and larger organisms, where the form of the whole structure is to be explained and/or simply described. Hence, in one of these domains, Thompson‘s approach is *reductionist*, and in the other, *holist*.

This internal inconsistency in Thompson's thinking will be discussed further

in our conclusions, see 7.4, Chapter 7.

It is also worth bearing in mind in the discussions to follow, that ‘description’ can be either *quantitative* or *qualitative.* Clearly any application of mathematics will fall in the former category if numbers, such as spatial measurements, are involved; but if the descriptions are more geometically or topologically based, the descriptive aspect could well be nonquantitative. Such mathematically based description (whether quantitative or qualitative) does not necesarily imply *explanatory power*, just *descriptive power.*

‘Descriptive power’, of course, lies at the roots of any form of classification or taxonomy, which in turn was a necessary precursor, without which the Darwinian theory of evolution by natural selection could not have come about. Just as explanatory models often start with measurement and/or calculation, so Darwinism had to start first with classification - an essentially descriptive process - though it might well, on occasion, depend on measurements such as length, mass, or discrete quantities (such as numbers of petals in a flower, or peas in a pod, say).

From such basic ideas, Thompson developed some ways of thinking which, due to their generality, have had a continued influence in diverse fields of research, not necessarily restricted to biology (*see also the Keller quotation, section 3.2, p50*). We next consider some of the concepts of most relevance to Developmental Biology, and first elaborate on the *quantitative versus qualitative dichotomy*, and its (rather complicated) relationship to the *explanatory versus descriptive dichotomy*, by examining another much debated dichotomy: *structuralism versus functionalism* .

2.1 Structuralism *versus* Functionalism

Though he did not, himself, use these terms, Thompson was addressing, by implication, the conflict between two schools of thought in the biological and social sciences - *structuralism versus functionalism.*

The terms *structure* and *function* are two of those conceptual (as opposed to technical) terms, which occur frequently in any biological discourse, with rarely (if ever) any attempt being made at a precise definition. It is interesting to find that both words are to be found in any dictionary of common usage, but may not be found in a specialist dictionary of biological terms. D.M.Lambert and A.J.Hughes (1988) [25] addressed this issue very well, by adopting an idea from R.Williams (1976) [26] who emphasised the interconnections between words that form a *logical cluster.* Lambert and Hughes preferred to use the related term *word field*, from I.Illich (1982) [27] . They investigated the pattern of relationships among some keywords in biology, by recording which words were defined in terms of each other in a common (rather than a technical) dictionary. They thus constructed a 'matrix of connections between [certain technical] keywords' which clearly separated into two fields (with a small degree of overlap). These served to distinguish between the conceptual terms *structuralism* and *functionalism.*

For instance, 'structuralism' corresponded to a word field containing {*whole, organic, organism, interaction, context, structure, organisation, homology, relationship*}, while 'functionalism' threw up a field containing {*function, purpose, character, fit, adaptation, natural selection, trait, variation*}.

Let us now formally define these two 'word fields' from the philosophical literature, so as to establish Thompson's position within the structuralist/functionalist dichotomy - or are these the two extremes in a continuum? (***See 2.1.3 below***).

2.1.1 Structuralism

In the philosophy of biology, *structuralism* is the belief that the form of an organism is governed principally by the physical forces at play in determining the changes in form of the embryo, and hence these forces are the principle determinant of biological form. This belief corresponds well with Thompson's basic premises as outlined in Chapter 1, and characterises him clearly as a structuralist. So, ***as outlined in 1.2 above***, structuralism puts Thompson at odds with the Darwinian idea that *natural selection* and *survival of the fittest* are the principal factors at work in governing the form of a species. Such factors would be essentially teleological, nonquantitative, and so descriptive in nature.

Our focus here will of course be on the place of structuralism (and of functionalism ***discussed in 2.1.2 below***) in the biological context, but it is important to note that both doctrines have had a much broader part to play in the history of philosophy, and of the social sciences and psychology in particular. (e.g. see D.P.Schultz and S.E.Schultz (2015) [28].) Clearly the above definition relates specifically to *biological structuralism*, an important contribution to which was made by Lambert and Hughes (1988) [25] in their paper *Keywords and Concepts in Structuralist and Functionalist Biology.*

Their own characterisation of structuralism is rather generalised in the extreme: 'Structuralism: The doctrine that structure rather than function is important'. Clearly, this can be interpreted in a very wide range of contexts, beyond the biological, but they go on to elaborate: ‘According to this viewpoint neither the elements nor the whole, but the relationship between them should be the focus of attention. Structuralism attempts to understand the laws and principles of organisation which represent the conceptual basis via which we can speculate about history.’ (G. Webster and B.C.Goodwin (1982) [29], and B.C.Goodwin (1982) [30], are cited in this context.)

Introducing ‘history’ here relates to the evolutionary (phylogenetic) development of life forms, and so the idea is in line with Thompson’s concern that there is more to understanding the ‘tree of life’ than Darwinian selection and survival of the fittest. (***See 1.2, p4 above.***) Webster and Goodwin (1982) [29] also make the point that ‘Structuralist biology attempts to explain the generation of actual structures from the range of the possible’. While R. Thom (1970) [31], stresses something of equal importance, that *stability* can be explained in terms of the organisation of the stucture itself.

An important insight arising from the above, ***which will be addressed further in Chapters to follow***, is that when we speak of particular biological structures being *stable* through successive generations, it is not the stability of the individual organism that is implied, since all individuals die. ‘The process to be explained is how structures are produced regularly in different generations.’ (Lambert and Hughes [25], p138.)

They also cite R. Thom (1975) [32] in this regard: ‘... we must not forget that the essential object of study in biology is not the isolated individual but the continuous form in space-time joining parents to descendants.’ Thompson would have appreciated this statement. In 1942 he made a fleeting reference to the relativistic concept of ‘space-time’ but overlooked its possible relevance to organismic development, remarking only on its suitability in the realm of the ‘infinitely great’ [e.g. in OGF(2), pp20-21]. However, on p283 , in concluding his Chapter III on *The Rate of Growth* he does state ‘In a newer language we might call the form of an organism an “event in space-time”, and not merely a “configuration in space”. (Here, the “double-quote” marks are Thompson’s own and, for obvious reasons, this sentence did not appear in the corresponding text, p154, of OGF(1) !)

Lambert and Hughes [25] p140, explain ‘structuralism’ succinctly, in a manner which resonates very well (though possibly unintentionally) with Thompson’s thinking: ‘... Structuralism is a “way of seeing” biology [their own quote marks] in which structures have time-extended properties and in which their dynamics result, not simply from an internal system, but also from external forces which are intimately associated with the developing individual. Consequently we view structuralism as encompassing the processes leading to the generation of both *deep structure* and *surface structure* or *form*.’

It was perhaps an oversight on Thompson’s part that he did not stress enough the above distinction between structure and form. It was his emphasis on the central importance of form (in the above sense of 'surface structure') to the developmental process, that led to the essentially descriptive character of the types of modelling which he advocated. ***e.g. see 2.3 below.***[1]

2.1.2 Functionalism

Lambert and Hughes(1988) [25], p136, defined functionalism as follows: 'A framework of thinking in which parts of the whole perform functions and these functions represent biological significance; and within an historical framework, leads to the notion of *purpose*. Consequently functionalism represents the view that structures result from a need posed by the *environment*.'

This definition has a similarly extreme generality to that of 'structuralism' above, but its references to 'purpose' (and by implication to teleology), and to 'environment', link it soundly to Darwinism (which in this context might be viewed as a special case), and this puts the doctrine at odds with Thompson. (***See 1.2, pp4 - 5 above.***)

This concept of 'function' in biology commits us to adopting associated keywords and concepts, such as those alluded to in the discussion of Illich's 'word fields', ***2.1, pp26 - 7 above***. Lambert and Hughes (1988) [25] saw the concept of 'function' in biology to be 'intimately connected to the [Cartesian] metaphor of living organisms as machines that are constructed from separate parts'. They go on to say, pp136-7, that 'This general view has canalised thinking in biology for centuries, and for example, heavily influenced the early stages of molecular biology during which Crick developed the so called "central dogma" [their own "double-quote" marks].' (***For more on this, see 3.5 below.***)

They go on to say that functionalism canalises thinking in two other significant ways:

An emphasis on 'parts' of organisms. Such as traits and characters, rather than upon the organism as a whole;

It leads to concepts of design, purpose, and teleology. 'Function when defined as "purpose" [their own "double-quote" marks] has no place in biological discourse. ... Darwin disposed of the conscious designer while retaining the concept of design. He rejected purpose for whole organisms but retained [it] for traits. This perspective also requires a quite inappropriate atomisation of the whole organism.' (Reductionism is implied here.)

This latter point, in relation to the concept of 'adaptation' in particular, is

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[1] 'Descriptive' here is to be contrasted with the mainly nonquantitative nature of description as it applies in the Darwinian approach to the origin of form. (*cf* the introductory paragraphs, pp25-6 above.)

developed further in 3.1 below.

Let us next consider, by way of an ideal counterpoint to the views of D'Arcy W.Thompson, those of a champion of functionalism, and a contemporary of Thompson (like him, also a Scottish fisheries biologist, and government fisheries advisor), Eduard Stuart Russell. He published the book *Form and Function: a contribution to the history of animal morphology* (383 pages) [33], in 1916 , the year before OGF(1) appeared. It is written, unlike OGF, in a style which would not be out of place in a modern treatise, and does not present so much descriptive morphological or anatomical detail. Instead, it is written from a much more philosophical standpoint, being more conceptually based.

His preface states his aims in writing the book very clearly, though his chosen terminology needs a little translation in relation to our discussion thus far: 'The main currents of thought are to my mind three - the *functional or synthetic*, the *formal or transcendental*, and the *materialistic or disintegrative*'. 'Functional' stands as above; 'formal' refers to the *formalist* tradition of comparative anatomy, an essentially descriptive discipline, which stands in the place of structuralism in the discussion above. His third brings in the concept of *materialism*, as a counterpoint to 'vitalism', and the 'disintegrative' epithet would be interpreted these days in the modern context of *reductionism*.

He goes on to describe 'functional' and 'formal' as 'these two opposing tendencies', the main 'battle-ground' for which is the ' ... problem of the relation of function to form. Is function the mechanical result of form, or is form merely the manifestation of function or activity? What is the essence of life - *organisation* or *activity*?'

His third 'current of thought' is instructive in blurring the boundary between the 'functional' and the 'formal' - in the above functionalist/structuralist dichotomy. 'The materialistic attitude is not distinctively biological, but is common to practically all fields of thought. ... the triumph of mechanical science in the 19th Century has induced many to accept materialism as the only possible scientific method. In biology it is more akin to the formal than to the functional attitude.'

He then declares his own position: 'In the course of this book I have not hidden my own sympathy with the functional attitude. .... I believe we shall only make progress [in understanding the real nature of life and organisation] if we frankly adopt the simple everyday conception of living things - which many of us have had drilled out of us - that they are *active, purposeful agents, not merely complicated aggregations of protein and other substances*.' We need go no further to appreciate why, in the light of subsequent developments in the biological sciences, D'Arcy Thompson's book enjoyed a more sustained readership and following than did Russell's, and why there is no significant cross-referencing between the two authors in their respective opuses[2].

2.1.3 Dichotomisation *versus* Unification

The title of Section 2.1, above, illustrates nicely what S.J.Gould (1986) [34] lightheartedly described as ‘playing dichotomies’, which he saw as a ‘favourite intellectual game whereby we simplify and caricature complex issues’ (as discussed by Lambert and Hughes [25]). My title above for this subsection 2.1.3, introduces a self-referential dimension to the concept of dichotomisation, and we shall have cause to play this dichotomies game in several places in the chapters to follow - ***e.g. see the contents list and, in particular, Chapter 5*** .

Gould saw structuralism and functionalism as one of the major dichotomies in biology, contrasting it with another such contentious field of discourse, *evolution versus creationism.* With regard to the former dichotomy, he claimed that an adequate theory of evolution [we might also add ‘biological development’ here] must ‘meld’ both approaches ... ‘by recognising the strengths of each vision’, and was thus arguing for a *pluralism* in biology comprising both structuralism and functionalism.

In Chapter 3, subsection 3.1.2, we will illustrate the value or weakness of this claim, with some empirical examples. The pluralistic viewpoint is, of course, implied in Thompson’s message IV, p7 above

However, the ‘evolution-creation’, dichotomy is clearly of a different order, and Gould had no wish to ‘meld’ (or *unify*?) its two components, on the grounds that, though logically consistent internally (within themselves), they are in this case incompatible, and could not be unified. Lambert and Hughes [25] saw such incompatibility to arise from differences in the ‘word fields’ (***see 2.1 pp26-7***) characterising the distinct systems of thought of which the dichotomy is composed. The degree to which ‘melding’ in Gould’s sense is possible would depend upon the degree of overlap between the respective word fields.

They took issue with Gould’s preference for ‘melding’ where possible, by claiming that *functionalism-structuralism*, and *evolution-creation* ‘do not represent dichotomies at all but rather four different “*ways of seeing*”. ‘ (Their own “double-quotes”.) They considered that such perspectives cannot meaningfully be ‘forced together’, since such ‘systems of thought have only an internally consistent meaning’. They cite the physicist D. Bohm (1965) [35] in the context of the *relativity versus quantum theory* conundrum: ‘[such uni-

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[2] Thompson makes one reference to E.S.Russell in a footnote, OGF(2), p167, concerning a paper on the growth of limpets. (There is no mention of Russell at all in OGF(1).) Russell refers once to D.W.Thompson in a footnote, [33] p2, citing the ‘interesting account of Aristotle’s biological work ... in the Herbert Spencer Lecture (1913) and his translation of the *Historia Animalium* in the Oxford Series’.

fication leads inevitably to] the confusion of trying to mix two sets of ideas that do not actually cohere.'

Lambert and Hughes offered the following advice, to help resolve the confrontation of such fundamentally different viewpoints in biology: 'We suggest that it is important for biologists to make their "way of seeing" clear to others. ... If we have the intention to communicate rather than obfuscate, our views should not be shrouded in mysticism [a lesson for creationists?] or difficult language [a lesson for Thompson?], but clearly outlined in order that they can best be understood'.

2.2 Growth as a Precisely Defined Concept

Thompson put forward very little in the way of a *unifying thesis* where organismic growth in general is concerned, but instead presented empirical data and growth curves for a wide range of organisms, including the familiar population growth curves for unicellular organisms such as yeast and bacteria. Hence, the material was presented descriptively, not so much by means of mathematical functions, as by the graphical or tabular presentation of data.

The findings of much subsequent empirical work underlined the futility of any attempt to find some single *growth controlling principle* in this context. (e.g. P. Weiss, *Chemistry and Physiology of Growth* (1949) [12].) C.H.Waddington, in *Principles of Embryology* (1956) [13] (p285), after discussing the range of processes involved in growth (and *degrowth*) prevailing among developing organisms, stated 'it is hardly to be expected that any very simple formula can fit all such cases'. He cites an equation of extreme *complexity*, involving over 12 different constants, each of which was supposed to be involved in the growth of a heterogeneous collection of tissues, such as in an embryo (the *Wetzel formula* (1937) [36]). Such a formula is so *complex* and so flexible, it can be made to fit almost any set of data. Waddington comments that the validity of such a formula would need to be sought in experimental justification of all its various components, arising from the postulated underlying processes, and 'We still know so little about the *unit processes* which go to build up the overall growth rate of an embryo for such an experimental justification to be provided'.

By 'unit processes' here, Waddington would have had in mind what E.S.Russell, in Chapter XVIII of his book [33] termed *causal morphology.* This was relatively novel at the time, and was an outcome of the more traditional current of *materialistic morphology* which in

Chapter XIV of [33], Russell described as ‘a movement [tending] towards the analysis and disintegration of the organism’. We would think of it as ‘reductionism’ nowadays. Causal morphology was essentially the origin of *experimental embryology*, led in the 1890s by a group of morphologists who sought the causes of form in an organism or species. Notable among them were Wilhelm His [37] p19; and Wilhelm Roux [38] p316, who coined the term *Entwicklungsmechanik* (*developmental mechanics*) for the new science. Its ultimate objective was to analyse developmental processes by breaking them down into *causal factors*, so as to provide a complete understanding of each stage of development. In Roux’s case in particular, this mechanistic perspective was intended to yield an understanding of the relationship between form and function in the developing organism. Thus the aim was to reduce the complex phenomena of life to lower levels of organisation.

Summing up his chapter III, on *‘The Rate of Growth’*, Thompson makes some very perceptive generalised comments, (OGF(1), p152). e.g. ‘ ... the characteristic form of the curve of growth in length (or any other linear dimension)[3] is a phenomenon which presents ... a definite and attractive problem for future solution’; and ‘[It seems that] the abrupt change in velocity [at points of inflection of the curve] must be due, either to a change in that pressure outwards from within, by which the “forces of growth” [take effect], or to a change in the resistances against which they act, [i.e.] the *tension* of the surface; and [by this we do not mean just] “surface tension” proper, but may extend to the development of a more or less resistant membrane, or “skin”, or even to the resistance of fibres or other histological elements, binding the boundary layers to the parts within’. (The *italics* and “double quotes” here are Thompson’s own.)

Among many other such insights he claims ‘... growth, while its own energy tends to increase, leads also after a while, to the establishment of resistances which check its own further increase’, and he cites (OGF(1) footnote, p153) empirical evidence to support this claim (Frazee (1909) [39]. He proposes, tentatively, that Frazee’s conclusion that small electrical current density, and low voltage, increases the rate of regenerative growth in tadpoles supports his hypothesis above, as ‘just such an electrification would tend to lower surface-tension, and accordingly decrease the [resistance to growth] of the external membrane’.[4]

On page 154, Thompson goes on to list his main conclusions on the rates of growth, ranging from those of tiny organisms ‘whose form, like that of a water-drop’, is due to the direct action of molecular forces, up to the phenomena of *regeneration.*

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[3] Thompson used terms such as ‘linear dimension’, or ‘linear measure’, in the sense of some measurement of length across, or within, a body or part thereof. Henceforward I will, preferentially, use the term ‘spatial measure’, so as to avoid possible confusion with the use of the term ‘linear’ in the mathematical senses employed in linear algebra or systems theory - ***as discussed in Chapter 6***.

[4] This is one of the few instances in OGF where Thompson cites experimental evidence to support his hypotheses. It illustrates the poverty and weakness of such evidence as was available to him at the time.

Two (of the eight) conclusions in particular comprise ways of thinking that are still in line with research efforts today:

Concerning growth without change of form 'Growth rates vary in an orderly way, ..., subject to definite laws. They differ in *degree*, and may be *graduated* [i.e. discerned as '*gradients*'], from one point of an organism to another; the rates in different parts and in different directions tend to maintain more or less constant ratios to one another in [a given] organism; and the fact that the form of the organism is in general regular and constant is due to the regularity and constancy of these relative growth rates.'

Concerning growth with change of form '... the ratio of velocities in different directions, though, is not absolutely constant, but tends to alter with time, or to fluctuate in an orderly way; the changes of form which accompany development, and the slower changes which continue in later life, are due to these progressive changes.'

Thompson admits that his rather descriptive discussion omits the role of the physiological mechanisms of the organism, '... by which growth is effected, and *controlled*'.

This leads, in effect, to Thompson's statement of a corollary to his message XII, *pp15-6 above* :

'We have dealt with growth in its relation to *magnitude*, and to that *relativity of magnitudes* which constitutes *form*; and so we have treated it as a study which stands at the *beginning of a morphological*, rather than the *end of a physiological* enquiry' (OGF(1), pp154-5). He goes on to admit : 'That is to say, we rule out *heredity* or any such concept not part of our present account, however true, however important, however indispensable in another setting ... , such a concept may be.'

In other words, growth *models* (not a term then in common scientific usage), based upon physical and/or mathematical principles alone, have a legitimate role to play, with or without the benefit of detailed knowledge of the fabric and functioning of life. This is an important feature of Thompson's thinking, and relates in particular to key messages VIII and IX in Chapter 1 above, intended for the consideration of experimentalist and empiricist workers, as well as mathematical modellers.

In considering many of Thompson's conclusions, we must bear in mind that much of his text was outmoded, even in 1942 when OGF(2) was published. Bonner, in his Editor's Introduction to the abridged edition of OGF(2), [5], commented that although there are minor deletions in all chapters (perhaps accounted for by the surfeit of new material in the 1942 edition - *alluded to in Chapter 1, p2 above*) there were six major omissions of whole chapters or sections. Foremost among these was the deletion (some might say censoring!) of the whole of Chapter III, *The Rate of Growth*, pp78-285 (a small book in itself), which Bonner deleted because:

a It was poorly organised and repetitive;

b There was too much emphasis on human growth, which was unhelpful in generalising to other forms of life;

c Thompson failed to appreciate fully the importance of *differential* or *relative* growth, now termed *allometry*, to which J.S.Huxley made notable contributions. It is strange that, although he discussed aspects of it in OGF in the most general of terms (e.g. see 'Concerning growth with change of form' above), Thompson made scant reference to Huxley's term, *heterogony*, for the phenomenon.

There are critiques along these lines by such eminent reviewers as E.W.Sinnott (1943) [40]; F.Mayer (1943) [41]; and P.B.Medawar [9], in his Postscript to Ruth D'Arcy Thompson's biography of her father [1].

For more current works on the study of rate of growth, Bonner refers the 'modern reader' (1961) to S.Brody, *Bioenergetics and Growth* (1945) [42], or J.S.Huxley, *Problems of Relative Growth* (1932) [43].

2.3 Allometry, and the Theory of Transformations

This concept, termed *heterogony* in Thompson's day, is the main subject of just one chapter (OGF, Ch.XVII), '*On the Theory of Transformations, or the Comparison of Related Forms*'. This is perhaps the best known part of the book, and it concerns (mainly) how the differences between the forms of related species can be represented geometrically, using transformations of systems of Cartesian coordinates. (Thompson termed this procedure the *method of coordinates.*)

(***See message XI, Chapter I, above, for further explanation of the method.***)

In many of the real examples Thompson illustrates, the transformations are not represented by mathematical functions, but by the empirical procedure of mapping anatomically homologous features between the Cartesian type and the other form(s) to be compared with it, and constructing the transformed coordinate system from this data, to enable the whole deformation of the type to be so mapped.

In Chapter 3, section 3.2, some more recent examples of the use of this procedure, and its limitations, are discussed.

Though this is interesting in a purely descriptive sense, as Thompson admits, there is little attempt at causal explanations for the transformations represented. It seems it was often sufficient in Thompson's eyes, simply to describe the nature of a morphological transformation, along with the rules underlying it. He was frequently less concerned about the details, or even the fundamental principles, of the mechanisms involved. All this is a reflection of Thompson's platonism *as discussed, Chapter 1, p13 under message XI.*

In fact, as a result of his indifference to causality here, Thompson himself offers some rather confusing discussion of embryological changes as opposed to taxonomic differences. e.g. in OGF(1), pp755-6, he gives one of his few developmental examples of allometry, involving the growth of a (fossil) plesiosaurian shoulder girdle, and its transformation between young and adult forms.

In Fig.2.3.1, the 'half-grown' form is presented as the Cartesian type on the normal Cartesian system, Fig.2.3.1 (left); and the adult 'full-grown' form is shown on the transformed coordinate system, 2.3.1 (right).

He next moves on to compare the above with the transformation from the shoulder girdle of the plesiosaurian to that of the (not closely related) Ichthyosaurus (Fig.2.3.2). The reason for such a switch from comparative morphology of developmental stages within a species, to comparative anatomy between species, is not made clear.

However, the famous *Recapitulation Law*, Ernst Haeckel (1866), e.g.[44], might well have influenced Thompson's thinking. (Haeckel was probably the first author to bring the term 'morphogenesis' into general use, and was regarded highly in 1917). 'Recapitulation' is the

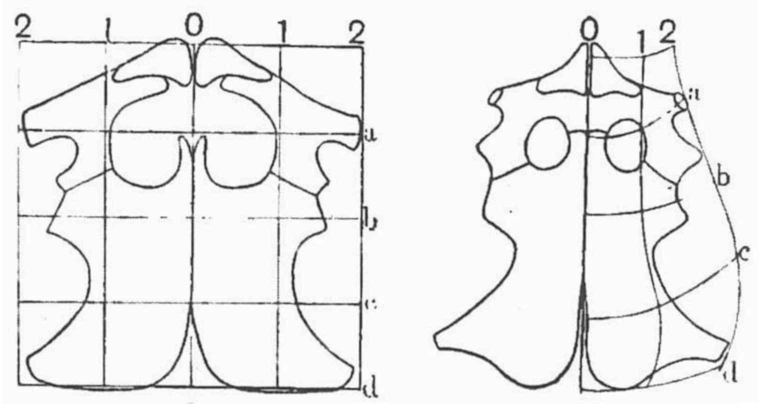

Figure 2.3.1: The ‘half-grown’ form of the fossil plesiosaur shoulder girdle (left), and the adult form (right), adapted from OGF(1), Fig.385

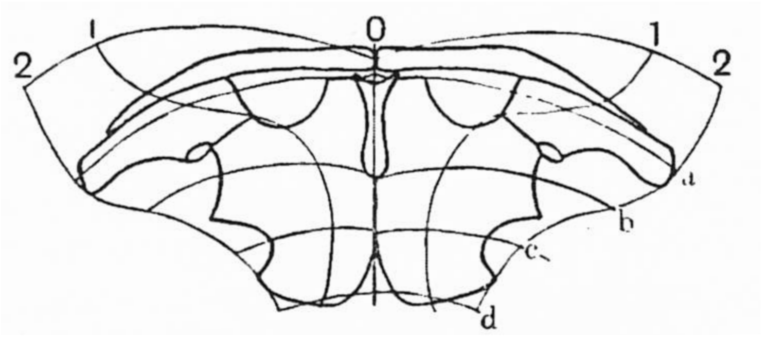

Figure 2.3.2: Fossil ichthyosaur shoulder girdle for comparison with plesiosaur forms above - adapted from OGF(1), Fig.386

(now somewhat outmoded) idea that living forms during their embryological development in some way display a sequence of morphologies reflecting their evolutionary development (famously stated in the literature as 'ontogeny recapitulates phylogeny'). Maybe this provided Thompson with justification for such comparative morphological statements, though possibly not in the specific instance discussed above.[5]

Thompson's remarks about the representation of form as a diagram of forces in equilibrium (message XI, pp13-5 above), also appear to confuse the phylogenetic aspects of changes in form (concerned more with the descriptive features of the transformation), with the ontogenetic (embryological) aspects, to which 'magnitude and direction of forces ... [converting] one form into another' is more relevant. The shortcomings of Thompson's theory of transformations suggested above, and in Chapter 3 below, in part explain why Thompson's work has not much featured subsequently in the mainstream of biological research, and it belongs very much a part of the descriptive tradition, in keeping with the era of its first publication. If there is a way forward for this methodology, it may yet stem from the recent emergence of *Comparative Developmental Genetics*, and the applicability of modern computer graphics to its techniques. (e.g. Adam C. Wilkins, *The Evolution of Developmental Pathways* (2002) [46]; especially Chapter 3, pp65-98, on *Comparative Molecular Studies*.)

Chapter 11 of [46], entitled *On Growth and Form: The Developmental and Evolutionary Genetics of Morphogenesis*, has a particular quotation (from R.D.K. Thomas and W.-E. Reif (1993) [47]), which resonates well with Thompson's ideas, but in modern day terminology: ' Organic form, constructed by developmental processes in individuals and transformed over time by evolution, cannot be fully explained by any one kind of analysis. If we are to understand morphology, results of experimental work in biomechanics, genetics, developmental biology and other fields must be integrated in the context of models based both on NeoDarwinian evolutionary theory and the *structuralist* assessments of the organisational potential of living systems'. ([46], p439.)

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[5] E.S.Russell [33], pp251-254 gives a fuller account of the origins of the law of recapitulation, which he traces back to Darwin himself in [6], through Fritz Műller in his *Facts and Arguments for Darwin* (1869) [45], and so to Haeckel's *Biogenetic Law*, first published in 1866 [44].

CHAPTER 3

Empirically-based Theories of Organismic Development

In the chapters and sections to follow, we consider a wide range of mathematical models of developmental systems (along with some computer implementations, and/or related simulations, as appropriate). In this chapter in particular, we outline how an increased understanding of biological developmental processes has emerged subsequent to the publication of *On Growth and Form.* This will demonstrate how modelling has come to reflect more realistically the real-world biology, as empirical knowledge and understanding have accumulated.

A helpful classification of developmental models was provided by E.F.Keller in her book *Making Sense of Life : Explaining Biological Development with Models, Metaphors, and Machines* (2002) [48]. Part One of her book discusses models which attempt to explain development 'without the help of genes'. In Part Two, Keller considers models incorporating our concept of the gene, which has increased in sophistication from the early 20th Century onwards.

Making use of Keller's taxonomy, let us now consider five classes of empirically-based models. The first three of these - *in Sections 3.1, 3.2 and 3.3* - will represent classes of model exemplifying Keller's 'gene-free' category. These are followed by two more classes - *in Sections 3.4 and 3.5* - to exemplify her 'gene-based' category of empirical model :

3.1 A brief look at Thompson's interpretation of form and function, considering the organism as a mechanical structure, in engineering terms;

3.2 Some attempts at applying Thompson's Theory of Transformations;

3.3 Evaluating Thompson's proposed programme of research within its twentieth century context - in particular the physico-chemical approach advocated in the work of Joseph Needham;

3.4 How genes came to be seen as developmental agents, and not just as mysterious 'factors of inheritance';

3.5 How genes came to incorporate the concepts of Molecular Biology.

3.1 How Thompson Interprets Form and Function Using Structural Mechanics

The subject matter of *On Growth and Form*, Chapter XVI, *On Form and Mechanical Efficiency*, lies in significant contrast to the contents of Chapter XVII and Thompson's Theory of Transformations - ***as discussed in 2.3 above***. In the latter case, Thompson is content to theorise in terms of Platonic *ideals*, considering forms in relation to well defined geometric shapes alone, while disregarding any concerns about *causation.* (***See also section 3.3.1, pp50-52, and the critical reviews cited there.***)

In Thompson's Chapter XVI, however, causation is very central to his ways of thinking. In Thompson's own words, OGF(1), p670; 'The phenomena which I have in mind [here] are just those many cases where *adaptation* [Thompson's own *italics*] ... is obviously present, in the clearly demonstrable form of mechanical fitness for the exercise of some particular *function or action* [my own *italics*] which has become inseparable from the life and well-being of the organism'. On p673 he goes on to say, 'The problems associated with these phenomena are difficult at every stage, even long before we approach to the *unsolved secrets of causation*; and for my part I confess I lack [the necessary knowledge] for even an elementary discussion of the form of a fish, ... insect, ...or bird. But in the form of a bone we have a problem of the same kind and order, so far simplified ... that we may ... find, in our partial comprehension of it, a partial clue to the *principles of causation* underlying this whole class of problems.' [1]

Thus, Thompson is indicating that his relative indifference to causation in such more

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[1] In the corresponding passage, p967 of OGF(2), Thompson substitutes 'phenomena' for 'problems' here.

theoretical models as he proposes in his Chapter XVII, *The Comparison of Related Forms*, may no longer apply if, rather than addressing the problems of form of an entire organism, we consider some particular and well defined part of the organism, such as a bone.

We should stress that his use of the words 'adaptation' and 'fitness' here is not to imply that Thompson is adopting a wholly Darwinian perspective, as in this context he is not relying exclusively on teleological and 'final cause' principles, but maintains his declared focus on the role of physical forces as explanatory principles. In OGF(1), pp672-3, he states (in opposition to the *final cause* approach) that there are such 'perfect adaptations of form which, for instance, fit a fish for swimming or a bird for flight. Here we are far above the region of mere hypothesis, for we have to deal with questions of *mechanical efficiency* where *statical* and *dynamical* considerations can be applied and established in detail.'

We should also stress that in many of the contexts which Thompson addresses here, there can be a blurring of the important distinction between 'adaptation' in the longer term evolutionary sense of preferential 'survival of the fittest' through processes of natural selection, as opposed to *physiological adaptation*, operating on shorter timescales, usually within the lifespan of an individual organism.

We next illustrate Thompson's approach to the problem of how form and function are related to the adaptation of bone to externally applied forces of stress and strain, and to the processes of growth and remodelling that take place in its development and repair.

3.1.1 Adaptation of Bone to Stresses and Strains

A mature bone has a complex architecture, in which dense plates of *compact bone* enclose cavities spanned by light networks of *trabeculae*, which are delicate shafts and buttresses of bony tissue, with soft marrow filling the spaces between. A typical *long bone* thus comprises a hard and stress-bearing outer region of compact bone, enclosing a lighter weight and weaker interior of *spongy bone* (or *trabecular bone*). (Fig. 3.1.1.)

It was well-known to Thompson that bone tissue can remodel itself in response to mechanical loads, such as *tensile* or *compressive stresses*, and that the trabeculae become

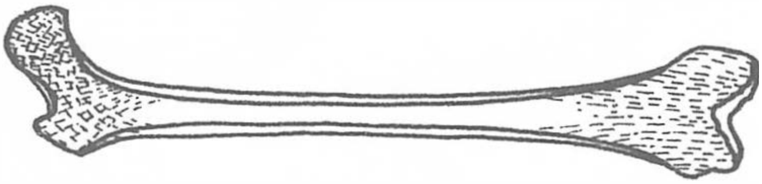

Figure 3.1.1: Diagram of a thigh bone (a typical long bone). From Fig.48 of P.S.Stevens *Patterns in Nature* [49]

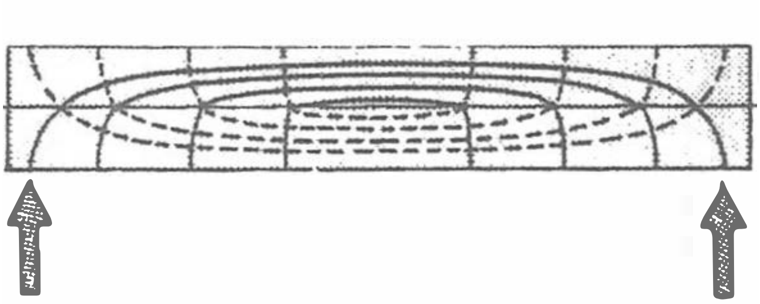

Figure 3.1.2: A beam subject lengthwise to uniformly distributed loads, showing lines of tension and compression. From Fig.47, ibid

oriented along the *principal axes* of stress within the bone. It was less well understood that, inspite of its rigidity, bone is not immutable, but effectively a living tissue. The *extracellular matrix*, impregnated with the hard calcareous mineral matter, is secreted by specialised cells called *osteoblasts*, which reside within a living network occupying channels and cavities throughout the matrix. These cells are now understood to enact a continual process of remodelling - while osteoblasts deposit new bony matrix, another class of cells, the *osteoclasts*, demolish old matrix. There is thus a mechanism of continuous turnover, and the possibility of replacement of bone matrix within and throughout the bone.

Fig. 3.1.2 illustrates the physical principles involved, adapted from Peter S.Stevens, *Patterns in Nature* ((1976) [49], p71. This shows a beam subject to a series of loads uniformly distributed over its entire length. The lines show the *trajectories of stress* within the beam, the lines concave upwards (dashed) depict the *trajectories of tension* and the lines concave downwards (solid) are the *trajectories of compression.*[2]

Around the middle length of the beam, lines of tension bunch together near the bottom edge, and lines of compression do so near the top. The closeness of the lines is a measure of the magnitude of the stress, and thus the diagram indicates that the stresses are especially high around the middle, diminishing as the ends of the beam are approached. Also, the

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[2] Thompson's preferred terms for the trajectories here were respectively *tension-lines* and *pressure-lines*, e.g. see OGF(1) p.686.

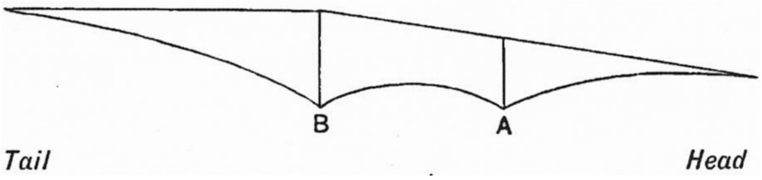

Figure 3.1.3: Stress diagram of dinosaur backbone, from OGF(1), p702

points where tension and compression trajectories cross lie along a line, called the *neutral axis*, running lengthwise along the centre of the beam. Along this line, the tension and compression forces cancel, and so no stress exists along the neutral axis.

This has the practical consequence that tubular structures can function with no, or reduced, load-bearing material along their central lengthwise axes. This in turn ensures their ability to minimise any loss in strength while increasing in size and/or losing mass. As is often the case in long bones, there is a benefit also in a thickening of the side walls along the central region of the structure, where the stress lines are most closely packed.

In this, and in manifold other ways evident within a skeletal structure, the “design” of a bone appears to be perfectly suited to its role and function, so the skeleton provides fertile ground for hypothesising along teleological lines. For instance, bone is thick and effectively load-bearing where stress is high, and thin where it is low.

To overcome this tendency for teleology to prevail at the expense of the mechanistic, the obvious question is ‘How does such adaptation in bone and the skeleton come about?’[3]

Thompson was only able to discuss this in very general terms. Thus in OGF(1), p711, he states: ‘... we see a tendency for material to be laid down just in the lines of *stress*, and so to evade thereby the distortions and disruptions due to *shear*.’ (The *italics* here are Thompson’s own.) (***See 3.1.2 below where ‘shear’ is discussed further.***) He goes on: ‘In these phenomena there lies a definite law of growth, whatever its ultimate expression or explanation may come to be. Let us not press either argument or hypothesis too far: but be content to see that skeletal form, as brought about by growth, is to a very large extent determined by mechanical considerations, and tends to manifest itself as a diagram, or reflected image, of mechanical stress. If we fail, owing to the immense complexity of the case, to unravel all the mathematical principles involved in the construction of the skeleton, we yet gain something, and not a little, by applying this method to the familiar objects of anatomical study ... .’ Numerous examples of such ‘diagrams’ are presented in OGF(1), pp690 to 709 (e.g. Fig. 3.1.3, adapted from Fig.348, p702).

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[3] In the case of a skeleton, as opposed to a single bone, there is an added need to think of bones as *compression members*, and the supporting ligaments as *tension members* - see OGF(1), p700, and Fig.345.

In his book *Patterns in Nature* (1976) [49], Stevens was in a position to cite some more specific hypotheses about the physiological adaptive powers of bone. Even now, those he cites may seem a bit archaic in light of more recently gained empirical knowledge about bone growth. For example:

- '... tensile and compressive stresses activate [in some way] *pressure-sensitive crystals* within growing material, and those crystals generate *electrical fields* that align electrically charged molecules and ions. Thus, the "coincidence" [Stevens' "double-quotes"] of lines of electrical force looking and behaving like lines of stress comes into play, and, through the agency of electrical forces, material gets laid down along the lines of stress.' (P.D.F.Murray (1936) [50]; and A.C.Bassett (1965) [51].)

- 'The control of growth in plants and trees is less well undersood, but electrical forces may again play a part. However they arise, "turbulent" forms [Stevens' "double-quotes"] are often materialisations of stress.' [By 'turbulence' here, Stevens alludes to the patterns often seen in the grain of timber, which resemble, and are seen as analogous to, a static image of turbulent flow in a fluid.] (Bruce I.H.Scott (1962), on *Electricity in Plants* [52].)

Hypotheses such as these reflect very closely Thompson's key message (***message X, pp11-13 in Chapter 1***) concerning the significance of forces, internal and external to the organism, in processes of development. ***See also section 1.4.1, p17 above, where force is discussed as a general principle in the determination of form.***

For a more current account of the growth and histology of bone, see Bruce Alberts *et al* (2015) [53], pp1229-1231.

3.1.2 Adaptation of Bone to Shearing Stresses

Let us stick with bone for now, as it illustrates very well some of the general principles arising in the making of hypotheses, along with any related experimental testing or modelling, concerned with growth, form and function.

In OGF(1), pp684 to 688, Thompson illustrates his modes of thinking, in coming up with hypotheses regarding the effects of *shearing stresses* in remodelling a bone, or the strengthening of stalks in plants. Some of the basic principles of shearing forces, as they apply to a loaded beam, bar or pillar, are:

- They produce *angular distortion* in a figure or form;

- There is no shearing stress along or perpendicular to the lines of principal stress (***as outlined in 3.1.1 above***), nor along lines of maximal compression or tension;

- Shear is nonzero on all other lines or planes, and takes a maximal value when inclined at 45 degrees to the cross-section.

In short, Thompson explains its relevance to living structures - in OGF(1), p686 - as follows: ‘ ..the danger of rupture or breaking down under shearing stress is lessened the more we arrange the materials ... along the pressure-lines and tension-lines of the systems; for *along these lines* (Thompson’s *italics*) there is no shear.’ Applying these principles to the growth and development of bone, he continues: ‘... we have only to imagine a litte trabecula (or group of trabeculae)[4] being secreted and laid down fortuitously in any direction within the substance of the bone. If it lie in the direction of one of the pressure-lines ... it will be in a position of comparative *equilibrium*, or *minimal disturbance*; but if it be inclined obliquely to the pressue-lines, the shearing force will ... tend to act upon it and move it away’.

He next reflects back on his conviction that genetics has no role to play in this process of (physiological) adaptation:[5] ‘In the biological aspect of the case, we must always remember that our bone is not only a living thing, but a highly plastic structure; the little trabeculae are constantly being formed and deformed, demolished and formed anew. *Here, for once, it is safe to say that “heredity” (Thompson’s “double-quotes”) need not and cannot be invoked to account for the configuration and arrangement of the trabeculae. For we can see them at any time of life in the making, under the direct action and control of the forces to which the system is exposed.*’ (My own *italics.*)

Thompson goes on to spell out the relevance of all this to bone regeneration and repair, and how in a matter of weeks the *trabecular system* will become entirely remodelled so as to fall in line with a new *system of forces.* In OGF(1), pp683-6, he cites (up to 1910) a number of authors who reported on the mechanical construction and adaptation of bone, including Julius Wolff (1892) [54] who observed that the above process of reconstruction extends ‘a long way off from the seat of the injury, and so cannot be looked upon as a mere accident of the physiological process of healing and repair’. That is, the reconstruction is a global process across the whole bone, or even across large components of the whole skeleton, and not just a localised injury repair.

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[4] Thompson seems to consider a ’trabecula’ to be some small building block (perhaps cell-like?). This is out of line with the modern - or even his contempoary - more anatomical interpretation - ***see 3.1.1 above.***

[5] When Thompson writes of ‘adaptation’, he often fails to make clear in a particular context, the distinction between the phylogenetic processes involved in natural selection, and purely physiological processes.

Thompson claims that the above phenomena support the case against functionalist explanation. 'Herein then lies, so far as one can discern it, a great part at least of the *physical causation* of what at first sight strikes us as a purely *functional adaptation*: as a phenomenon, in other words, whose *physical cause* is as obscure as its *final cause* or *end* is, apparently, manifest.' (OGF(1), pp687-8.) Thus he admits that, given the state of knowledge in 1917 (and again in 1942), any attempt at physical explanation must be 'obscure', but no more so than the merely 'apparent' explanation provided in functionalist (and 'final cause') terms.

The above passage reflects Thompson's key message IV, p7 above, which stresses the need for unification of mechanistic and teleological principles, if a full understanding of developmental phenomena is to be achieved. It also relates to arguments for pluralism, as spelled out in section 2.1.3, p31.

In the light of modern knowledge, and in particular that of epigenetic phenomena (*see Chapter 4 et seq*), we can question Thompson's hypothesis. Moreover, we must not confuse adaptation within and between species, in the Darwinian sense, with the physiological adaptation that takes place within an individual, as in injury repair discussed above.

However, Thompson did have a further explanatory trick up his sleeve, concerning the role of *strain*. He described its significance here as the 'physiological truth that a condition of *strain*, the result of a *stress* [Thompson's *italics*], is a *stimulus to growth itself*.' (My *italics*.)

He illustrated this with a nice Thompsonian anecdote: 'This is indeed no less than one of the cardinal facts of theoretical biology. [e.g.] The soles of our boots wear thin, but the soles of our feet grow thick, the more we walk upon them: for it would seem that the living cells are "stimulated" [Thompson's "double-quotes"] by pressure, or by what we call "exercise" ["ditto"], to increase and multiply'. (OGF(1) p688.)

We might comment that yes, there is a physiological adaptation to be described or explained here, but from our current day perspective Thompson overlooks the likelihood that the cells' capacity to respond in this way may well be explained by 'invoking heredity' .

Space here does not permit me to explore other examples of physical phenom-

ena which Thompson employs in the generation of hypotheses about growth, form and function, and the possible models to be derived from them. Suffice it to say that many of the considerations illuminated by Thompson's examples of stress, strain and shear, also become apparent in his treatments of *turbulence, flow, least effort, surface tension, close packing and much more, but most importantly, the constraints of three-dimensional space.*

To conclude this section, it is worth highlighting one specialist area in which Thompson's ideas have been applied in a very practical way. George J. Armelagos *et al* (1982), p317 [55], take up Thompson's interpretation of *form* and *function*, which employed a descriptive analysis of structure based on *statics* as used in Civil Engineering. This approach views the organismic body as a machine that, during the course of its own activity, must accommodate to the forces of *stress* and *strain* imposed. In this way, Thompson had outlined a basis for *biomechanics*, and *functional anatomy.* This became much used in anthropological studies of human origins and evolution. The key point was that, since function influences growth, then form is linked both causally and temporally to function (*Ibid*).

3.2 Attempts to Apply Thompson's Theory of Transformations

By Conrad Waddington's time [13], Thompson's ideas had not been much studied, but one area of interest that did soon attract attention was to apply the *method of transformations* to the comparison of developmental stages of a single species. As the overall growth concept (***see section 2.2 above***) had already proved difficult to quantify meaningfully, attention soon switched to the *relative growth of parts* (e.g. see [13], pp287 *et seq*), which acquired the name *allometry.* Essentially this defines, for some linear (i.e. spatial) measure, the magnitude, $\mathbf{x}$, of the whole organism, as a function of that of a correspondingly defined magnitude, $\mathbf{y}$, of some part of the organism[6].

In Fig. 3.2.1, **A** shows the log weight of the two distal segments (crosses) and the two proximal segments (circles) plotted against the log weight of the middle segment (the carpus) of the claw of the fiddler crab *Uca.* The slopes of these lines define the *allometric growth constants.* **B** shows the gradients in growth constants along the claw in *Uca* (solid line), and in the spider crab (dashed line).

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[6] See footnote 3, Section 2.2, p33 above.

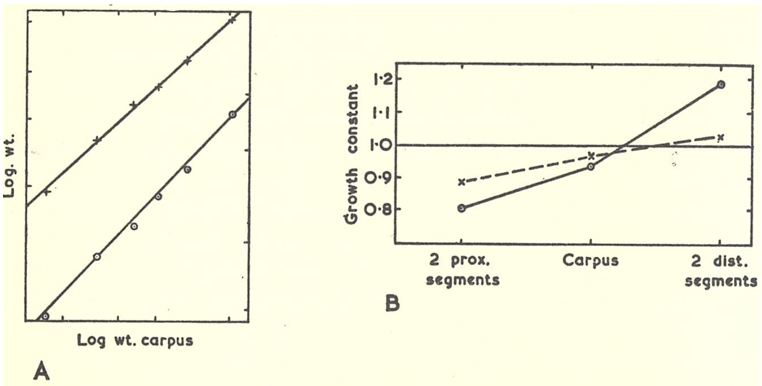

Figure 3.2.1: Examples of growth curves - from Fig13.3, p.288 of C.H.Waddington [13]. See text for explanation.

Many real examples were reported, showing how the growth rates of parts (with respect to time **t**) within some complex body structure, relative to that of some standard part, vary in a graded manner between locations within the structure. Simple expressions of this were reported, e.g. by J.S.Huxley (1932) [43], Le Gros Clark and P.Medawar (1945) [56], and Reeve and Huxley (1945) [57], in the series of limbs attached to different body segments in crustaceans. For such sets of comparable parts, an allometric growth constant, **a**, in Figure 3.2.1, can be determined for each part. Such a variation in constant, **a**, is taken to define a *growth gradient.* The discrete jumps in growth gradient in the above examples easily generalise to the idea of a *continuous growth gradient.* This is most simply observed in the growth of a single mass, thin film, or layer of tissue, where the gradients usually show a continuous gradation, determining the ultimate form the tissue takes up.

Thompson's *theory of transformations* (***2.3 above***), in particular regarding the transformation of forms in the ontological context, clearly has a bearing here. His distortions across a coordinate system produce alterations (transformations) within any inscribed figure, which are continuously graded as, very probably, will be the corresponding growth gradients.

Conrad Waddington, [13], p292, remarks that Thompson's work potentially 'opens up a large field for investigation', but that 'little has been done to make [Thompson's method of transformations] into a means of exact analysis'. He cites Medawar (1945) [58], as taking some steps in this direction, by studying the changing shape of the human body from the early foetus to the adult. (See Figure 3.2.2.)

The procedure adopted was as follows :

- Simplify the body to a 2D shape, representing it as a series of outline drawings viewed from in front ;

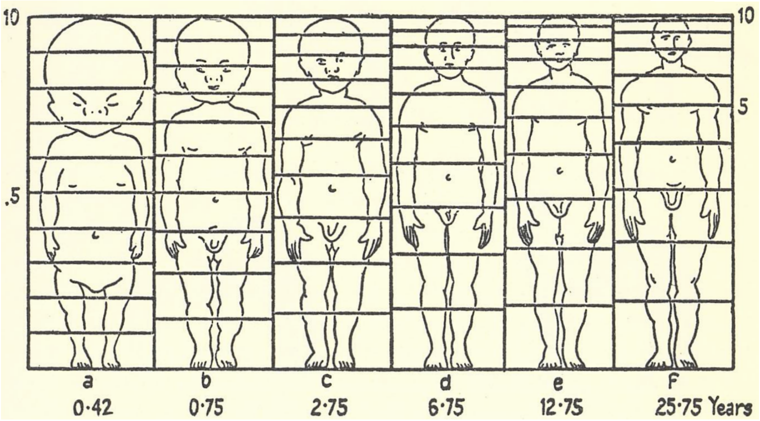

Figure 3.2.2: Changes in the proportions of the human body during growth. From Fig.13.5, p293 of C.H.Waddington [13]

- It appears there is a single continuous growth gradient, with its highest value at the feet, falling off steadily with increasing height towards the head ;

- Simplify the body form further by considering a selected number of 'landmark' points on the vertical midline e.g. foot, groin, navel, nipples, chin, etc., thus reducing a 3D form to a line with these intervals marked on it ;

- Let P_1, P_2, P_3, etc, be the respective heights from foot to groin at successive times; Q_1, Q_2, Q_3, etc, be the respective heights from groin to navel at the corresponding times, and so on ;

- Represent this gradation in the separation of the marked intervals algebraically, as a coordinate transformation, by deriving *empirical equations* deduced from measurements of the the actual values of successive P_i's, Q_i's, etc ;

- Algebraic relations can then be derived between the equations relating to the P's and those relating to the Q's, the R's and the S's, etc ;

- The two sets of equations so constructed enable the whole series of transformations from early foetus to adult to be expressed algebraically.

However, Waddington himself criticised the value of such a procedure, commenting, [13], p292, that 'Such labour is only justified if it enables one to see certain relations which would otherwise be missed. So far [1956], such evidence of a real usefulness of the method has not been forthcoming.' Other reservations were voiced concerning the applicability of Thompson's particular style of physical and mathematical models to problems in biology. (***e.g. see further comments of Waddington under 3.3.3, pp54-5 below.***)

For more recent work on allometry and growth in humans, see Stephen J. Gould, *Allometry and Size in Ontogeny and Phylogeny* (1969) [59]; F.W.Went, *The Size of Man* (1968) [60]; and J.T.Bonner, T.A.McMahon and J.Tyler (1983) [17].

Reservations such as those alluded to above in part explain why actual use of such models in the subsequent history of theoretical biology has been very limited. This serves only to deepen the mystery of how it is that a very large book about bio-mathematical theory could (even nowadays) be considered a milestone in 'popular science'. However, we must not forget that D'Arcy Thompson was a multidisciplinary scholar, whose writing appealed to a wide audience. E.F.Keller [48], p.54, makes the point very well: 'It is precisely this multiplicity of concerns that has lent Thompson his appeal to such a diversity of readers: his interest in construction arouses the sympathy of bio-engineers; his interest in the aesthetics of form attracts the attention of artists and architects; and his interest in mathematical formalism invites contemporary mathematical biologists to claim him as the forefather of their discipline.' An excellent recent account of the wide-ranging influences on the visual arts (of the illustrations in OGF in particular) is given by Matthew Jarron (2015), in *A Sketch of the Universe - the Visual Influences of D'Arcy Thompson's On Growth and Form* [61].

3.3 The Place of 'On Growth and Form' in the Contemporary and Subsequent History of The oretical Biology

It is worth our while at this stage, briefly to appraise Thompson's place in the history of biology, in view of the actual trajectory this history has followed since the publication of OGF(1) and OGF(2). Let us first look at some reviews of both editions (*3.3.1*), whilst here, and in later chapters, we will attempt to clarify the intellectual connections with other notable figures in biophysics or biochemistry, starting here with the eminent biochemist and chemical embryologist, Joseph Needham (*3.3.2 below*).

3.3.1 Some Reviews of Both Editions of *On Growth and Form*

In a recently published discussion of Thompson's programme, E.F. Keller (2018) [62] notes that if the choice were between as yet unidentified mechanistic explanations as opposed to mysterious vitalistic descriptions, Thompson unambiguously opted for mechanism. She remarks that already in 1917 'vitalism was on the rout'. However, a more measured view might be appropriate here: even if the battle was in principle won inside the biological community, in the cultural world beyond, the debate was still very much alive in 1917. ([18], p6.)

Indeed, reviewers of OGF(1) saw his work explicitly in this light. In *Science*, for example, the Canadian anatomist, J.P.McMurrich (1917) [63], explicitly referring to vitalism states: 'The contest between the vitalistic and mechanistic views of the phenomena of life has been carried on generation after generation ... and always with the strategic results of the struggle in favor of the mechanists, as one vitalistic stronghold after another has fallen. The attack is drawing ever nearer to the central citadel and Professor Thompson's book is a massing of the attacking forces before the citadel'. Hence, as with other reviewers of the time, McMurrich praised the central philosophical thrust of OGF(1), and its engaging style.

Both editions attracted the attention of distinguished reviewers, as was noted by both Keller [62] and (in another recently published discussion) S.Wolfram [64].

However, the long-awaited OGF(2) disappointed reviewers, both on philosophical and biological grounds. For instance, J.W.Wilson (1944) [65], wrote a review worth reading as a biological essay in its own right, as a philosophical reflection on the state of biology in the mid-twentieth century. He criticises Thompson not only (in common with many other reviewers) for the absence of genetics, but also for his so-called *Platonism*, which implicitly promotes *idealism* as opposed to 'workman-like' *empiricism*: Quoting Wilson, '[Thompson] thinks of form as a Platonist. In his discussion of the tortoise shell, for example, he [talks of] an ideal tortoise, more valid than any actual specimen or species, and any variant from which may be considered an "accident" [Wilson's double-quotes].' Wilson continues: 'In the Epilogue [Thompson] aligns himself with the teaching of Plato and Pythagorus, and again says, "In natural history Cuvier's 'types' [which are Plato's ideals under another name] may not be perfectly chosen nor numerous enough, but types they are; and to seek for stepping stones across the gaps is to seek in vain, forever".'

Other aspects of Thompson's Platonism, and its impact upon how his contemporaries received 'On Growth and Form', can be found under 'message XI', p13 above (on the significance of the term 'form' as used in OGF), and in section 3.1, p40 above.

Wilson's mixed review (which included kinder sections explicitly praising the style and the pro-mathematical philosophical stance) was not alone. In the *Journal of Physiological*

Zoology (1943), J.W.Buchanan (the journal's editor) [66] compliments the beauty of the prose, and the learning of the author, but adds:

'The reviewer regrets that he is compelled to raise some more or less important criticisms of this long and exquisitely prepared volume. In his prefatory note Professor Thompson says that the book needs no preface since it is all preface. The reviewer would go further and point out that some of the chapters of which the volume is a preface have already been at least partially written but no referencee to them is to be found. The vast evidence of the relation of hormones and similar agents to organic growth and form receives scant attention. Nor does the more recent study of the relation between molecular configuration and form and structure receive the hopeful treatment it merits. Moreover, the entire field of the genetics of form is passed by with little comment, and the work of the experimental embryologists and students of regeneration seems to have been overlooked entirely ... . No doubt American readers will be surprised at the omission of significant American literature and the absence of names familiar to every modern student of form determination.'

In the Sections and Chapters to follow, we will encounter numerous figures who have contributed new approaches to developmental biology, some at odds with Thompson's approach, others that can be seen, at least implicitly, to develop or elaborate his ideas. Most of these contributions emerged subsequenty to OGF(2), but one figure worthy of note in the (mainly inter-war) years between 1917 and 1942, was that of Joseph Needham. Let us next consider briefly how his approach was in many ways to have greater impact than Thompson's.

3.3.2 The Place of Joseph Needham in Twentieth Century Biology

A fuller account of Needham's work is to be found in [18] (pp11-12), from which this subsection is partially extracted.

Buchanan's criticism (***3.3.1 above***) of Thompson's OGF(2) was true, of course. His narrative on the development of the organism was not readily recognised by the new breed of biologists - concentrating as they did on the properties of cells, and even the chemistry of cells, in which organisms showed remarkable commonality - rather than on the whole gamut of different forms of organisms, which gloried in diversity. For them, the mid-20th century figure in the new science of embryology would almost certainly be Joseph Needham. His two encyclopaedic contributions - his three volume *Chemical Embryology* (1931) [67], and his follow-up 757 page *Biochemistry and Morphogenesis* (1942) [68] - sit astride the field of developmental biology, transforming the developmental process from *deus ex machina* to complex biochemistry amenable to the experimental method. For example, it was Needham, among others, who showed that Hans Spemann's (1924) [69], embryological *organiser centres* need not be interpreted within a vitalist framework, but by contrast had a chemical origin. Although Cambridge University Press published editions by both Thompson and Needham in 1942, it seems reasonable to guess that to the practical biologist, it was Needham's careful exposition of experimental method, rather than Thompson's prophetic vision, which was more useful.

Needham was interested in mathematics as an amateur, and he does seem to have been influenced by Thompson at various key stages of his career - e.g. see Erik Peterson (2016) [70], on the *Theoretical Biology Club and the Roots of Epigenetics*, and Stephen Hyde (2013) [71], on *Thompson's Legacy in Contemporary Studies of Patterns and Morphology.*

But in general, Needham's writings do not include much mention of mathematics, yet somehow the spirit of his work was nevertheless calling out to the mathematical profession, as witnessed by the remarks of the Chicago mathematician A.S.Householder [72] (1944) in the *Bulletin of Mathematical Biology*:

'... with even a casual reading of the book [Needham's *Biochemistry and Morphogenesis*] one finds many places where quantitative theoretical formulations seem called for ... . such terms such as "competence", "determination", "potency", and the like [***see also 3.4 below for further such terms***], are so clearly in need of quantitative, rather than qualitative, treatment that a feeling of impatience is hard to suppress ... . It is not necessary to comment on the important role that must be played in the development of the subject by such a comprehensive outline by an outstanding authority in this field. Mathematical biophysicists in particular, will find it invaluable when they undertake any work on problems of development.'

3.3.3 Thompson's Contribution in the Pre-molecular Era of Developmental Biology

The work discussed in section 1.4 on the physico-mathematical principles highlighted by Thompson (pp16-23); and that on allometry, discussed in sections 2.3 (pp35-38), and 3.2 (pp47-50) above, all represent aspects of the *pre-molecular era* where developmental studies are concerned.

However, these topics were all motivated from the viewpoint of physicists or mathematicians, in an era prior to the 1980s, before genetics and molecular biology came to dominate thinking within the biological community itself.

Before moving on to how mathematical modelling has progressed since the 1980s, it is worth taking stock of where biological thinking in the field of developmental processes stood, in the pre-molecular era.

A key figure in this era was Conrad Hal Waddington, whose *Principles of Embryology* (1956) is a classic in its field, and is still in print [13]. This book summarises the state of knowledge in embryology up to the stage where the physical nature of the gene in biochemical terms started to become clear, with the elucidation of the structure of DNA. (See also, sections 3.4 and 3.5 below.) In our present context it is worth paying attention to Waddington's view of the contribution of D'Arcy Thompson in this premolecular era.

The criticisms of OGF in relation to its lack of genetics, and its tendency towards platonism are already discussed above (***e.g. see under 3.1, p40***). Such criticisms came mostly from physicists, biochemists, and mathematicians, but Waddington's reservations were more those of an embryologist of the time. They arise in Chapter XX of [13], concerned with the formation of *pattern and shape*, an aspect of development termed *individuation* in the literature of the time. He distinguished this from *differentiation* ('the production of new substances - be they simple ones, such as pigments, or complex, such as the various types of tissue'), as opposed to 'the arrangement of these substances into definite relative positions, and, usually, the moulding of them into characteristic shapes'. [13], pp415-6. These days we might think of individuation as comprising the two elements of *pattern formation* and *morphogenesis.*

On the positive side, Waddington (p432) states: 'By showing that many animal forms share certain mathematical properties with shapes that are known to arise in the inorganic world, [Thompson] had a most important influence, both in persuading biologists that form offers a problem which should be analysed in causal terms, and in making it seem not too impossibly difficult for such an analysis to be carried out'. However, his reservations arose on a number of issues :

1 Thompson's analogies and metaphors contributed nothing to the task of understanding, 'which remains for the future';

2 His work dealt only with one special class of forms - 'those of simple cells and of small groups of cells';

3 He was fond of explaining pattern and form in terms of surface tension in liquid films, but this seems irrelevant in the light of knowledge of the cell membrane, which even before 1942, ceased to be considered a liquid;

4 Further to the above, Waddington proclaimed that: 'Even if one accepted his discussion, ... still one would be forced to admit that the principles discussed throw little light on the *initiation* [my own *italics*] of a pattern such as that of a pentadactyl limb';

5 Another special class of morphogenesis that Thompson emphasised was that of 'forms that arise from particular types of differential growth, such as [that of] the shell of the gastropod ... to be twisted into a spiral. ... interesting though this is, it leaves unsolved the fundamental question of how the pattern of differentiatial growth rates arises in the first place'.

So it seems that the embryologist of Thompson's era (even in that 'premolecular age') could not be satisfied with Thompson's platonism, which often put the description of form as paramount, to the (possibly inadvertent) neglect of causal explanations inaccessible in Thompson's era. Waddington summed up well his problem with Thompson's approach as follows ([13], p432): 'The most essential problem of form is one which cannot be approached by a mathematical analysis of the ways in which animal shapes become transformed during development. It is the question of how form originates from the formless, and demands either an experimental attack or a mathematical analysis of a different kind, perhaps similar to that begun by Turing'.

We will consider the work of Alan Turing, and other such 'kinds of mathematical analysis' in Chapters 4, 5 and 6, and also look in more depth at the questions of differentiation and pattern formation, in Chapter 5 in particular.

For now, let us start to examine, in Sections 3.4 and 3.5 below, how the subsequent 20th century history of the subject focusses on biochemistry and its offspring, molecular biology. But it is worth noting here that mathematicians and chemists often talk a different spiritual language. What constitutes intellectual organisation for one, is for the other mere verbiage, or worse, deliberate obfuscation. For some, equations and mathematical concepts are great simplifiers, while for others they rather hide the obvious in a mass of incomprehensible squiggles. The evolutionary biologist S.J.Gould (1971) [73], a great populariser, but neither mathematician nor chemist, averred that molecular biology alone could not replace the 'concept of form and spatial structure', and it was the latter which was Thompson's main concern.

3.4 How Empirically-based Models in Developmental Biology Came to Involve Genes as Developmental Agents

As J.B.L.Bard (2008) [74] points out, 'the standard view of embryologists in the 1930s ... was that development proceeds under its own momentum and genes merely fine-tune events by, for example, determining eye colour'. This view could still be found in textbooks in the 1980s. Before anyone had any clear idea about what a gene was, or how it functioned, the main focus of attention in experimental embryology was the interaction of tissues, and the chemical agents which mediated these interactions. *Inductive interactions* between tissues in contact were forefront among these, and the big interest was how the amphibian neural tube is *induced* by contact of mesodermal cells in the dorsal lip of the gastrula, with the ectodermal cell layer. The fact that this *neural tube induction* could be effected by a limitless range of arbitrarily chosen chemical agents (or even foodstuffs !), brought the realisation that the search for *inductive signalling agents* between the interacting tissues, was misguidedly seeking an answer to a wrongly framed question.

Waddington, who was working on embryonic induction in the 1930s, realised that his subject needed a paradigm shift, and in the process was to invent the new field of *Developmental Genetics.* As Bard points out, 'Waddington was the first developmental geneticist, and probably the most important developmental biologist of the pre-molecular age'.

However, it is worthwhile our briefly reviewing the embryological concepts which arose in this 'pre-molecular era', as many of them involve simplifications in the ways of thinking about complex systems, which could lend themselves to mathematical modelling or simulations. (***cf the quotation from A.S.Householder, 3.3.3, p53 above.***) Much of the terminology used in describing the role of cell and tissue interactions in embryonic development (*embryogenesis*), is due to Waddington himself, and is well reviewed by J.B.L.Bard (2008) [74]. Many of the terms introduced in the 1920s and 1930s, were in Waddington's words '*operational terms*' as they were labels for classes of experimental outcomes of tissue interaction. *Induction, evocator and organiser action, regulation, cell fate, cell and tissue differentiation, individuation, pre-patterning, determination, equipotentiality, equifinality, and organogenesis* were all examples of this, as was *tissue competence* (a term introduced by Waddington himself in 1932 [75]). Such terms were useful shorthand for macroscopic phenomena deemed to be effects of tissue interaction, but (as Waddington (1962) [76] observed) they failed to help with our understanding of the 'underlying elements' involved in such 'operations'. Bard (2008) [74] and Stern (2000) [77] highlight the continued utility of some of the many terms Waddington either introduced or redefined for understanding development, including '*epigenetics, canalisation, creods, regionalisation, homeorhesis, pattern formation*, and *trajectory*'. In Bard's words [74], '...Waddington more than any other developmental biologist produced the words that shaped the agenda

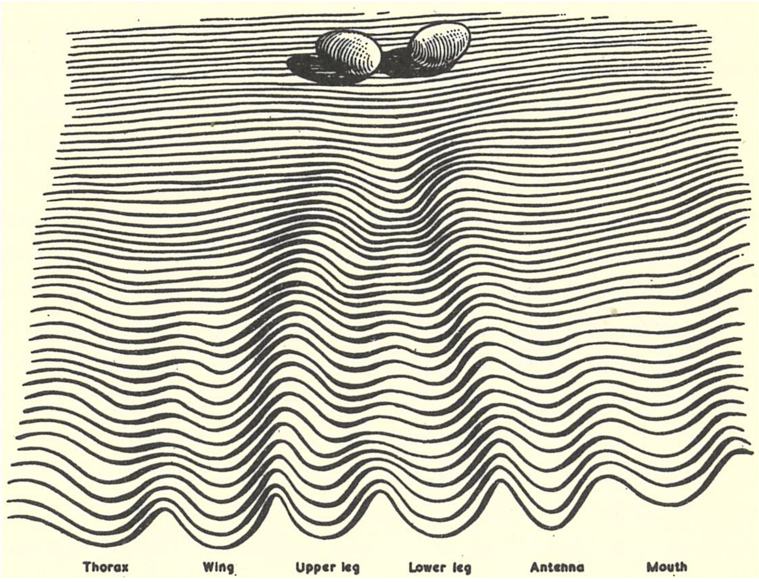

Figure 3.4.1: The epigenetic landscape. From Fig.16.2, p351 of C.H.Waddington [13]

of development between 1940 and 1980'.

Some of Waddington's own terminology is used to explain two of his 'big-picture' concepts - *epigenetics* and *epigenetic landscape. Epigenetics* (not to be confused with *epigenesis* - ***see Chapter 5, 5.1.1***) is the process by which genes manifest themselves through the *phenotype.* In more modern systems theoretic and 'molecular' terms, it is the translation of information encoded in the genotype into phenotypic characteristics. The word arises from blending the terms *epigenesis* and *genetics*, and it brought genes into the picture. Waddington was the first to realise that development of the phenotype results from the combined processes of genetic expression, and tissue interaction - that genes underlie phenotypic activity.

The idea of an *epigenetic landscape* is, in Bard's characterisation, 'a graphical metaphor' (Fig. (3.4.1). In Waddington's own words ([13], p351 and Fig.16.2), 'It is ... a symbolic representation of the developmental potentialities of a genotype in terms of a surface, sloping towards the observer, down which there run balls each of which has a bias corresponding to the particular initial conditions in some part of the newly fertilised egg. The sloping surface is grooved, and the balls will run into one or other of these [*bifurcating*] channels, finishing at a point corresponding to some typical organ.' This is from the original account in Waddington (1940) [78]. He arrived at these ideas through his own studies of the developmental genetics of wing venation patterns in *Drosophila melanogaster*, using mutant forms of wing patterns, which showed how the various mutant genes affect the patterns. In these studies he spoke of how the normal *trajectory* of an *embryonic region*, can be modulated by particular gene mutations to enter other trajectories (or *'canalised paths'*), thus determining different *cell fates* or *'states of cellular differentiation'* for the embryonic region under study.

Thus, the above embryological concepts, through Waddington's innovative ideas, came to involve the concept of the gene, but only in the sense that genes must be some form of agent which determines the appearence of particular phenotypic characteristics, by mechanisms as yet unknown. Further advancements in developmental biology awaited discovery of the role of the gene as an agent with a regulatory function, and this could only come about with the emergence of a new discipline - ***Molecular Biology.***

3.5 How Gene-based Models of Development Came to Incorporate the Concepts of Molecular Biology

Classsical genetics, up to about 1960, depended on the vague idea of *gene action*, as there was no clear idea of the physical nature of the gene, how it operates physically or chemically, nor of the causal connection between presence of a gene in the genotype, and how it effected the corresponding phenotypic characteristics. This began to change with the disclosure in 1953 of the double helical structure of DNA, by J.D.Watson and F.H.C.Crick [79] in their classic paper in *Nature*, *Molecular Structure of Nucleic Acids and Structure of Deoxyribose Nucleic Acid.* It was soon established that the DNA in genomes is not itself directly responsible for the direction of protein synthesis, but the closely related RNA (*ribose nucleic acid*), acts as an intermediary. If the cell requires a particular protein, the appropriate segment of the DNA is *transcribed* into the necessary *complementary* strand (or strands) of *messenger RNA* (mRNA) comprised of a suitable sequence of nucleotides (in the process termed *transcription*). The mRNA copies of DNA segments are used as *templates* to direct the synthesis of the protein (in the process called *translation*). The flow of *genetic information* in cells is therefore from DNA, to RNA, and so to proteins. Each type of amino acid from which protein strands are assembled is encoded (within the now famous *genetic code*) by a particular sequence (a *triplet*) of three of the five nucleotide bases which make up DNA and RNA molecules. A full account of the above principle, which came to be known as the *central dogma* of molecular biology is to be found in any modern textbook on Cell Biology - e.g. *Molecular Biology of the Cell*, by Bruce Alberts *et al* (2015) [53].

The growing knowledge of the roles of DNA and messenger RNAs (mRNAs) in the production of proteins determining phenotypic characteristics was first incorporated into genetics through the work of J. Monod and F.Jacob (1961) [80]. The gene was now identifiable as a particular region (*nucleotide sequence*) of a double-stranded DNA molecule. Jacob and

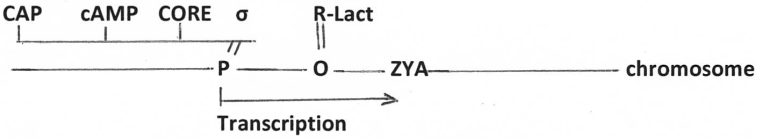

Figure 3.5.1: Schematic diagram of the lactose operon. Adapted from Fig.11.1, p415 of S.A.Kauffman [81]

Monod were the first to recognise the distinction between *structural genes* and *regulatory genes.* The former code for proteins which have either some structural role to play within the organism; or some role in the assembly of metabolically active proteins such as enzymes, with a functional role. In contrast, the regulatory genes in some way regulate the action of other genes. This conceptual change concerning the roles of genes originated the discipline of *molecular genetics.*

Jacob and Monod achieved this through studying the genetics of bacteria - in particular *Escherichia coli*, whose rapid rate of reproduction, by the simple *fission* of bacterial cells, enabled so many generations to be observed in a manageable time, that *genetic loci* on the DNA strands could be mapped at a much finer scale (i.e. at a higher *allelic resolution*) than in slower reproducing types. If a gene activating a particular structural gene is situated very closely nearby to it on the DNA strand, then it is possible to find relatively rare mutant forms in which the activity of the regulator gene, rather than that of the (regulated) structural gene, is in some way altered. It is a relatively straightforward matter to predict possible phenotypic effects in such a scenario.

They called their particular model the *lactose operon*, involved with metabolism of the sugar, lactose, in the nutritional medium of *E. coli.*

In general, an operon is a length of bacterial DNA, comprising a sequence of contiguous genes that is *transcribed* into a single messenger RNA molecule. This mRNA becomes (in general after editing into shorter lengths) *translated* into the set of amino acid sequences which ultimately comprise the set of protein products of the operon. The *operator*, O, is a short region of DNA, that controls (e.g. turns on or off) the transcription of an adjacent gene or operon. The *promoter*, P, is a nucleotide sequence in DNA, which acts as a *binding site* for the enzyme *RNA polymerase* which catalyses the transcription of genes in the corresponding operon, into their corresponding mRNA nucleotide sequences. The act of binding initiates the process of *transcription.*

In the lactose operon in particular (Fig.3.5.1 above) O is the *operator site*, and P the *promoter site.* (This figure is adapted from S.A.Kauffman, *The Origins of Order* (1993) [81].) Z, Y and A are the structural genes coding for proteins involved in lactose metabolism.

The operon is read from left to right by the RNA polymerase enzyme, which *transcribes* the DNA nucleotide sequences for Z, Y and A into the corresponding mRNA *transcript.* For this operon, the particular mode of operation is as follows, where R is a *repressor protein* which binds with O :

- When R is bound to O, transcription is blocked (*repression*), unless R itself is bound to *allolactose*, an 'allosteric variant' of the lactose molecule;

- When allolactose binds to repressor molecule R, the latter's conformation is changed, and this change releases it from operator O (*derepression*);

- P is regulated by four molecular factors: cAMP (cyclic adenosine monophosphate - an energy source); CORE, a 'core enzyme' necessary for RNA polymerase to become active; σ, a factor which binds to CORE, enabling it to effect transcription; and CAP, a factor which binds to cAMP;

- All four of these **trans-acting factors** must be present for the initiation of transcription.

Jacob and Monod, in their paper (1961) [80], concluded that, in what we now call the *operon model*, 'The discovery of regulator and operator genes ... reveals that the genome contains not only a series of blueprints [i.e. genes determining the structure of enzymes and other proteins], but a coordinated program of protein synthesis and the means of controlling its execution'. So they were the first to propose the existence of a *genetic program*, thus launching the field of *molecular genetics*, and converting the primitive notion of 'gene action', to a new way of thinking about development - the genetic program. (e.g. see E.F.Keller (2002) [48], pp135 *et seq*, for a more in depth, and philosophical account of this historical development.)

Of course, the term 'genetic program' is in itself rather a vague concept, and the question also arises as to whether the operon model can be applied to the more complex forms of development seen in multicellular organisms. To pursue these issues further, we need next to consider some parallel developments arising from the fields of Systems Theory, and Cybernetics (*Chapter 4 below*).

CHAPTER 4

Cybernetics and Systems Theory

Fritjof Capra and Pier Luigi Luisi (*The Systems View of Life* (2014) [82]), trace the origins of modern *systems theory* to the early 20th Century school of *organismic biology* (or *organicism*), established in reaction to the concurrent trend towards *reductionism* - the belief that all properties and functions of living things should be explicable in terms of chemical and physical laws. Organicism elaborated the ideas of earlier schools of philosophy (e.g. from Aristotle), advocating the holistic view, that the reductionist approach contributes little to our understanding of how structural subunits and their functioning (e.g. at the subcellular level and above), are coordinated to achieve an integrated functioning of the cell, or organism as a whole.

Contemporaneously with D'Arcy Thompson, the little known Russian medical researcher, Alexander Bogdanov, published the three volumes of *Tektology* (1912-17) [83]. This was in effect the first attempt at formulating a general systems theory (see [82], pp84 - 86). 'Tektology' translates as the 'science of structures'. Bogdanov very foresightedly posited that for all systems (he also used the word 'complex', as a noun, synonomously with 'system') their stability and development can be understood in terms of 'two basic organisational mechanisms - *formation* and *regulation*'. In developing these ideas he used language which is not out of place in modern 'systems thinking'. For instance, he spoke of how 'organisational crisis' manifests itself as a breakdown of the existing 'systemic balance' and simultaneously represents a transition to a new 'state of balance'. ([82], p85.) ***See Chapter 6, in particular***, for how this translates into modern conceptualisations and terminology, e.g. in Complexity and Catastrophe Theories.

Systems theory became a major scientific movement, inspired by publication of a series of papers (1940-66) by Ludwig von Bertalanffy. An organismic biologist, his viewpoint is well conveyed (in [82], p86, and cited from L.v Bertalanffy, *General System Theory* (1968) [84], p37), as follows :

'General System Theory is a general science of "wholeness" ... . In elaborate form it would be a mathematical discipline, in itself purely formal but applicable to the various empirical sciences. For sciences concerned with "organised wholes" it would be of similar significance to that which probability theory has for sciences concerned with "chance events" ["double-quotes" are Bertalanffy's own].'

He also addressed the paradox that living things develop, and/or evolve, towards increasing order and complexity, while being subject, like all physicochemical systems, to the second law of thermodynamics. He made the distinction between *open systems* and *closed systems.* While the latter move towards a state of thermal equilibrium, living things are open systems, and cannot be described just by classical thermodynamics. He characterised living systems as 'open' because they can only develop, or stay alive, by means of continual flows of matter and energy to and from their environment. Unlike closed systems, open systems must maintain a *steady state*, far from equilibrium. He postulated that a new thermodynamics of open systems would be needed to model them.

But in the 1940s, the mathematical tools were not available to extend thermodynamic theory in this way. *In Chapter 6 below*, progress in this direction, in particular through the work of Ilya Prigogine, and Complexity Theory, is discussed.

The *Cybernetics movement* developed independently from the above, through militarily funded research during WWII. 'Cyberneticists' comprised a multidisciplinary community of mathematicians (e.g. John von Neumann and Claude Shannon), engineers, neuroscientists (e.g. Warren McCulloch) and social scientists. Engineer Norbert Wiener [85] (1948), coined the word 'cybernetics' (derived from the Greek for 'steersman'), and defined it as the science of 'control and communication in the animal and the machine'. Biologists, of course, would prefer to use the more general epithet 'organism' rather than 'animal'.

Cyberneticists sought more abstract and generalised levels of description than did the concurrent systems theorists and organismic biologists. They studied patterns of communication, especially in *closed loops*, and *networks.* This led them to the characteristically cybernetic concepts of *feedback*, *self-regulation*, and (later) to *self-organisation.* ([82], p87.) ***See also, 4.4 below***.

Cybernetics came to have a major impact on the further development of *systems thinking*, and *systems biology* - the modern successor to organismic biology.

We next review the framing of problems, and what characterises systems theoretic or cybernetic models in developmental biology, leading to the key developmental concept of *self-organisation*.

Since adoption of the term 'systems biology' modern usage has relegated 'cybernetics' to become a rarely used and outmoded term in biology. So in what follows we will consider cybernetic and systems theoretic modelling to be synonymous as far as developmental biology is concerned, while recognising the key role the cybernetics movement played in the origins of systems biology both in general, and in the developmental context.

4.1 Framing Problems of Developmental Biology in Systems Theoretic (or Cybernetic) Terms

M.J.Apter (1966) [86], in a book devoted (possibly uniquely) to the consideration of cybernetic/systems theoretic approaches to the study of biological growth and development, considered that these 'might be of particular use in this field, since developing systems are complex ones which are difficult to understand without reference to *principles of organisation*'.

Clearly the conjunction of the term 'systems' with the qualifier 'developmental' here, requires some further consideration, since it implies a special class of 'system' with characteristics adding complexity to the usual concept of 'system'. This in turn requires the construction of appropriate types of model when it comes to conceptualising or simulating such systems.

Early Definitions of Systems These were manifold, but vague. e.g. Apter ([86], pp7-8), cites Bertalanffy (1952) [87], p11: 'A complex of elements in mutual interaction'; and W.R Ashby (1956) [88], p40: 'A list of variables". (***See also Bertalanffy's distinction between open and closed systems, p62 above.***) Ashby further defined the particular systems of interest in cybernetics to be those 'that are open to energy, but closed to information or control'.

Elaborations of the Systems Definition Apter ([86], p6), claimed that 'Cybernetics is concerned with systems at the level of *organisation* and *information*, rather than with the properties of the *fabric* of which the particular systems are made except insofar as these affect the organisation'. This reflects our quotation from D.W.Thompson, (***in 2.2, p34 above, and also messages VIII, IX and XII in Chapter 1***). Apter goes on to evoke the *'levels of organisation' doctrine*, originating from the Gestalt school of psychology, which states '... the living organism can only meaningfully be dealt with at a higher level than physics and chemistry, and at this level, quite new phenomena *emerge* which are of the very essence of such *self-organising systems*, and which are missed at any lower level.'

(***The idea of emergence implied here will feature significantly in Chapter 6 below.***)

The idea of *non-decomposable systems* as suggested above, was expressed more formally by Paul Weiss (1963) [89] as follows :

'If **a** is indispensable for **b** and **c**, **b** for both **a** and **c**, and **c** for both **a** and **b**, [then] ... a system of this kind can exist only as an entity or not at all.'

The Particular Contribution of Cybernetics to Systems Theory This was summed up in the most general terms by W.R.Ashby (1956) [88], p7) as follows :

'Cybernetics envisages a set of possibilities much wider than the actual, and then asks why the particular case should conform to its usual particular restrictions'. This 'top-down' approach is a significant change from the familiar 'bottom up' approach met with in scientific investigation, of breaking a system down into its components, in order to understand the whole. The latter approach will frequently fail in this regard, and also in any attempt to understand the functioning or role of the constituent parts within the whole system. By contrast the 'whole system' (or *holistic*) approach starts with a *classification* of possible non-decomposable wholes, and asks why the actual system fits one or other, in particular, of the elements of this classification.

Apter (1966) [86], p7), extended this idea to recognise two aspects of cybernetics :

- the *syntactic*, concerned with the principles governing all possible systems (Ashby's greater interest), and

- the *semantic*, concerned with the relationship between these principles, and the particular naturally occurring systems being studied by empirical scientists.

Apter claimed that 'syntactic cybernetics' corresponds closely to von Bertalanffy's General System Theory, and so in his view, and contradictory to modern usage, cybernetics encompassed systems theory.

4.2 Characterising Systems Theoretic/Cybernetic Models, and their Relationship to Mathematical Models

4.2.1 Effective Dynamic Systems and Models

In all these methodologies, the aim is to describe *real systems* in terms of some *formal system*, and in arriving at such descriptions, to use these in the *explanation* of the functioning of the real system.

The distinction here from the methods of D'Arcy Thompson is worth noting here, as most of his methods tended to stop at description only, in the absence of any unifying principles which could provide anything in the way of explanations.

M.J.Apter [86], p9 *et seq*, discusses the notion of an *effective dynamic model* - a type of formal model which has proved of particular utility in the modelling of developmental processes, and lends itself to mathematical formulation - ***discussed further in Chapters 5 and 6 below***. The following adapts Apter's characterisation, so as to relate it more specifically to mathematical modelling :

- A *system* (and its description also) is *effective* if, with only a knowledge of its *state* at time **t**, and the sequence and times of the inputs into the system from time **t** onwards, it is always possible to predict the changes of state at each time step, and its final state (if any);

- To achieve this, the time interval must be chosen so as to give a description of state transitions sufficient to resolve the system behaviour to an appropriate level of detail;

- The time interval might be vanishingly small if the system behaviour can be represented by a continuous function or functions;

- Otherwise the state changes should be charted in a stepwise fashion, usually subject to instructions in the form of *conditional decision procedures*;

- There must be no contradictions in the sense that the same 'instruction' yields different results at different time-steps, under conditions that are, for it (the instruction), identical;

- However, the system as a whole might well function in such a way that the same input to the system at a given instant produces different results, depending on the previous *history of inputs to the system.* If the latter applies, then the system is described as *dynamic*;

- A *dynamic system* is to be contrasted with a *linear system*, such as one which may be represented graphically by a one-to-one curve, in which the same output is always generated by a given input.

We next consider some particular contributions from the old cybernetics, which have come to play an increasingly central role in elaborating the modern theory of developmental systems.

4.2.2 Feedback-loops and Self-regulation

One of the main achievements of cybernetics, which has had a lasting effect on systems thinking, stems from N. Wiener's comparison of organisms and machines [85] - leading to the *mechanistic modelling* of living things, which finally put to rest any hint of vitalism in theoretical biology. This success resulted from Wiener's concepts of *feedback* and the *feedback loop.*

F.Capra and P.L.Luisi [82], p89 *et seq*, define a feedback loop as 'a circular arrangement of causally connected elements, in which an initial cause propagates around the links of the loop, so that each element has an effect on the next, until the last "feeds back" the effect into the first element of the cycle. So the first link (the '*input*'), is affected by the last (the '*output*'), resulting in *self-regulation* of the whole system, due to modification of the effect each time it travels around the cycle'.

Commonly this idea is expressed in terms of *information* - e.g. 'the conveying of information about the outcome of any process or activity to its source' (***ibid***).

A century was to elapse before the connection between such '*circular causality*' and the feedback embedded within self-regulating machines was recognised. (***See Fig.4.2.1***

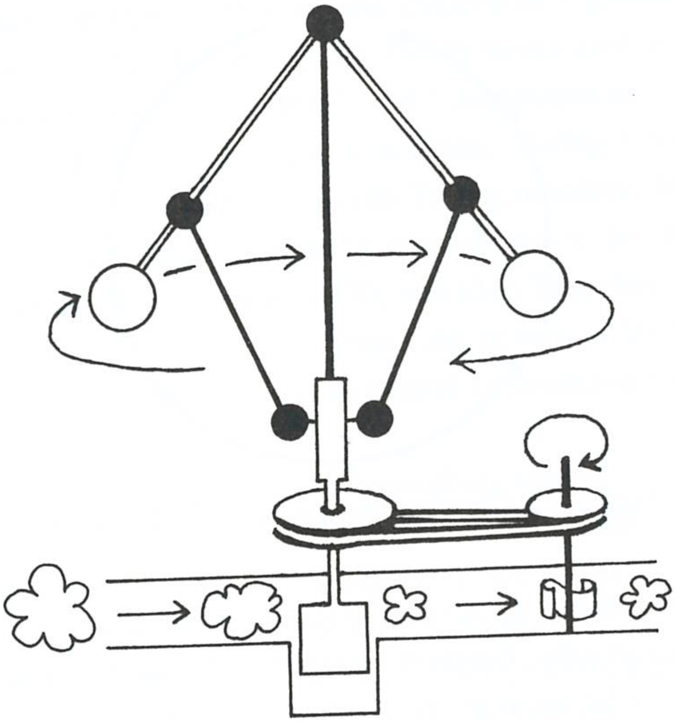

Figure 4.2.1: Diagram of the Watt's Governor, illustrating how understanding the embedded 'pattern of circular causality' is not very straightforward. From Fig.5.2, p90 of F.Capra and P.L.Luisi [82]

above.)

It was Wiener *et al* who made the further connection to living organisms, by recognising that feedback was the essential mechanism behind *homeostasis*, a term introduced by Walter Cannon (1932) [90]. This is the process of self-regulation within organisms, that enables them to maintain their state of *dynamic balance.* Cannon described many self-regulatory metabolic processes, but as with the control engineers before him, did not recognise the existence and significance of the closed causal loops embedded within his self-regulating systems.

As Capra and Luisi point out ([82], p91), ' Today we understand that feedback loops are ubiquitous in the living world, because they are a feature of the *nonlinear network patterns* that are characteristic of living systems'. (***Further discussed in Chapter 6 below.***)

Systems theorists now recognise the existence of *positive*, as well as *negative feedback loops.* The former may be considered *self-amplifying*, and the latter *self-balancing.* It is such systems theoretic concepts arising from cybernetics and engineering control theory that were needed to develop further the idea of a 'genetic program' alluded to in our discussion of the operon model of Jacob and Monod (***in 3.5 above***).

4.2.3 Two Significant Early Examples of Effective Models in Developmental Systems Theory

The mathematician and logician Alan M.Turing (1952) [91] working independently of the cybernetic school, presented a model under the title ‘ *The Chemical Basis of Morphogenesis*’, which showed how a fairly regular pattern can emerge from an initially homogeneous *unstable* system, subject to random disturbance (or *perturbation*). He makes the following simplifying assumptions :

- Consider a 2-dimensional sheet of tissue, arranged as a ring, to avoid complications from boundary effects;

- Assume only two substances are involved, diffusing through the tissue, and reacting chemically so as to generate or destroy one another;

- Assume a situation such that the system reaches an *equilibrium*, in which the substances are spread homogeneously throughout the tissue.

Next, he assumes hypothetical values for the *rates of diffusion*, and *rates of reaction.* He then shows that for particular cases, if a substance appears (by chance) to reach a sufficiently high concentration at certain locations, then its concentration will continue to increase. Thus the substance will diffuse outwards from this location, leading to enlargement of the region of high concentration.

Turing went on to show that under some conditions, a *periodic wavelength* (formed by alternating regions of high and low concentrations) can emerge throughout the whole system. The wavelength will be a function of the input values of diffusion and reaction rates.

The significance of this ‘*reaction-diffusion model*’ (and of the whole class of models inspired by it) to developmental biology, was this *emergence* of a *pattern* from an initially homogeneous system. Pattern formation *per se* does not comprise ‘morphogenesis’, but the hypothesis that such a pattern could underlie the subsequent formation of structures did justify Turing’s claim that this models the chemical basis for morphogenesis.

The biological credibility of Turing’s model has meant that it has retained its significance through to the current day. However, biologists were quick to express reservations, as is often the case with mathematical or other formal classes of modelling. For instance C.H.Waddington (1962) [76] considered the main drawback in Turing’s model to be that the pattern formed does not adjust to changes in scale of the overall system. i.e. if the system becomes larger (as in a growing organism), the parts of the pattern do not increase in proportion. Instead the number of elements in the pattern (e.g. stripes) would increase. Thus in Waddington's view, the model is good for explaining relatively superficial patterns, such as the dappling of pigments on insect wings, but could not explain the development of the underlying patterns involved in, say, the formation of organs.

Turing's model is based on continuous mathematical functions, and so the time intervals involved are treated as vanishingly (or *infinitesimally*) small, in the language of differential calculus. Our second example, based on discontinuous (*discrete*) time steps, was devised jointly by W.A.McCulloch (a neuroscientist), and Walter Pitts (a mathematician) (1943). Their model has come to be known famously by the epithet, *'Neural Networks'* [92]. Both of these authors were pioneering members of the cybernetics movement proper.

Though devised with the modelling of neural networks in mind, the emergence of ordered patterns in its outcomes again made it germane to developmental biology. Idealised neurons were represented by *binary switching elements*, and the model represented a nervous system or its components by *complex networks* of such elements. This layed the foundations for one of the key aspects of *complexity theory*, ***which we discuss further in Chapter 6 below***.

In such *McCulloch and Pitts Networks*, the 'on-off' nodes are coupled such that the activity of any node at time **t** is determined by the preceding activity of other nodes, according to some *switching rule.* For instance, a node, **N**, may switch 'on' or 'off' only if a specified number of adjacent nodes are 'on' at time **t**. McCulloch and Pitts showed that, though they were simplified idealisations of real networks embedded within the nervous system, they approximated well to them.

4.3 Concepts of Information, Pattern and Complexity

In 1949, C.E.Shannon and W. Weaver published *The Mathematical Theory of Communication* [93], thus establishing what is now known as *Information Theory.* This complemented N.Wiener's publication (1948) [85], on control and communication. Whereas Information Theory relates to the work of the communication engineer, the Automata Theoretic aspects of Wiener's book concern more the work of the computer engineer.

We have already demonstrated the relevance of the latter to developmental

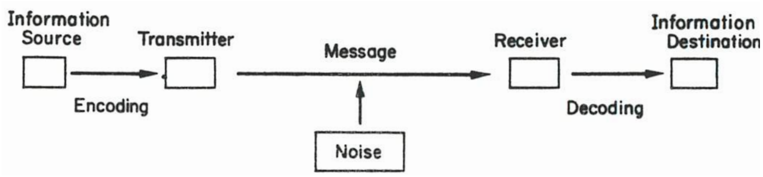

Figure 4.3.1: Schematic diagram showing the flow of information in a communication channel. From Appendix 2, p178 of M.J.Apter [86]

processes (*4.1 and 4.2 above*), insofar as it addresses the logical aspect of *dynamic systems.* Up to the mid-1960's the apparent relevance of Information Theory to developmental biology also aroused much interest, especially when the empirical theorising turned to concepts such as *genetic information, information transfer, genetic coding*, and *genetic programs - 3.4 and 3.5 above.*

4.3.1 The Information Theory of Shannon and Weaver

Shannon and Weaver established a precise mathematical way of determining how best to design a *communication system.* The familiar way of representing such a system is shown in ***Fig.4.3.1***.

The *coding* process involves translation of an *alphabet* of *letters* comprising the *message* at the *source*, into a code of *binary digits.* Each letter is represented by its own unique string of 1's and 0's, each such digit being termed a *bit* of *information.* Of course for any given alphabet, there have to be sufficient bits in each binary string to enable coding of all distinct letters in the alphabet.

They derived the following expression for the average amount of information (in terms of bits) in each letter :

$H = -\Sigma p_i log_2 p_i$ **Eq 1**

where p_i is the probability of occurrence of each letter L_i in some finite alphabet. By analogy with the use of the term *entropy* in statistical mechanics, H came to be known as the *entropy* associated with the selection of any string comprising a message. ***Fig.4.3.1*** indicates the presence of *noise* affecting the coded message. The significance of noise is that the probability of the received message being correct is reduced to some value p,

$0 < p < 1$.

An important outcome of the theory was the idea of using *redundant information* to help overcome the effects of noise, and reduce the *error* in the transmitted messsage. One simple way to introduce *redundancy* is to duplicate each bit in the encoded message. e.g. in a 3-bit binary code, if a letter is represented by the string (001), then it could instead be represented by the string (000011). The redundant bits provide a measure of protection against extraneous interference in the signals, but this is at the cost of halving the *transmission rate*, T. If the *maximum possible transmission rate* is T_{MAX}, then a measure of the *transmission efficiency*, E, is :

$E = 1 - T/T_{MAX}$ **Eq 2**

Shannon defined T_{MAX} for a given *noisy channel* as the *channel capacity*, and showed that in principle redundancy can make any message perfectly reliable using such methods of *error correction.*

As far as its relevance to developmental biology is concerned, the same ideas do not have to apply to an alphabet of, say, Roman letters. The object of study could be any communication system involving finite sets of symbols or signals, the selection of each of which could be assigned a probability value. Given that any such selection can be considered as an '*event*' then, more generally, any circumstance involving selection from a finite set of events, each with an assigned probability, lends itself to the Shannon approach.

It is important to understand that Information Theory has nothing to do with the content (or meaning) that the message conveys, since it only concerns the relative probabilities of 'events' - such as selection of symbols or signals. Failure to recognise this has often led to misinterpretations of how Information Theory might apply to developmental (or other complex) processes.

4.3.2 Elaborating the Ideas of Information Theory

Given the above measure of information, attempts were made to address the following questions (see C.J. Apter [86], p77) :

1 Can we ask how much information there is in an organism at any time ?

2 Can we compare the amount of information in the same organism at different times during its development ?

3 If Information Theory can be used in these two ways, can it elucidate the classical developmental problem of *preformation versus epigenesis* ? (See ***5.1.1 below.***)

Most of these efforts foundered, because any method of defining an 'alphabet' for development was based partly on guesswork, and partly on arbitrary choices of features (e.g. structural, molecular, genetic) to identify with 'letters' in the alphabet. In addition, estimates had to be made as to the relative probabilities of occurrence of the postulated 'letters'. S.M.Dancoff and H.Quastler (1953) [94], p263), two of the leading investigators in this field, admitted that they had put forward 'crude approximations and vague hypotheses' [but that their estimates], 'though extremely coarse', [are] 'better than no estimate at all'. However, M.J. Apter and L.Wolpert, co-authors of Ch.4 of [86], believed that 'on the contrary, [their estimates] are probably not better than no estimate at all, since such estimates are liable to be misleading' (p80).

The demise of such lines of investigation came about because of the realisation that confusion prevailed about the precise nature of the 'communication channels' under consideration. For instance, in seeking an answer to question **2** above, simple comparison of the 'information content' of, say, the zygote, with that of the adult organism, was really making use of two independent channels - zygote to observer, and adult organism to observer. This had nothing to do with the true communication channel to be studied - that linking the zygote to the adult.

One worker with a more credible viewpoint was Chr. P. Raven (1961) [95]. In his view (concerning sexual reproduction) the egg (ovum) is the *communication channel*, the parents are the *information source*, and the individual arising from the fertilised egg (zygote) is the *destination* of the information. (***Fig.4.3.1***) In these terms information is *encoded* during the formation of the gametes and subsequent fertilisation (fusion of sperm and egg cells). *Development* is then a process in which the information is *decoded.*

Raven needed to explain how, whilst the zygote contains much less information than the adult, the latter results from the decoding of the information in the zygote. His explanation was that the extra information in the adult is *redundant information* - ***cf 4.3.1 above***. That which remains unaltered in the adult, Raven called *specific information.*

Wolpert and Apter, among many other criticisms, saw the main shortcoming of the information theoretic analysis of development to be that the chosen methods of measuring information ignore 'those qualities that are generally accepted as being the significant features of a developing, rather than a simply growing, system' ([86], p82). [Furthermore], ' ... the original Dancoff and Quastler definition of the amount of information in an organism concerned itself only with the *specification of parts with no reference to their interrelationships*'. They saw this as equating the amount of information in a pile of rubble with that in the previously constructed building; a meaningless jumble of letters with the Shakespeare sonnet composed from them; or a living animal with the same animal after homogenisation.

On p84, the point is made more abstractly - 'Just as *meaning* is not taken into account by the Shannon-Weaver theory of information, so *shape, spatial pattern*, and *organisation* are not taken into account in the [information theoretic approach to development].'

So the implication is that an understanding of development requires not just a measure of increase of information, but a measure of an increase in *organisation* or *complexity.* (e.g. H. von Foerster (1960) [96], pp31-50.)

Following on from this, Wolpert and Apter query 'whether development is in any sense a decoding problem. It would seem to be more nearly a *deductive process*, and this is rather different.' (***cf 5.3 below on L-systems and languages***, and the distinction between a *genetic program*, and a *genetic grammar*.) Their criticism also highlighted the fallacy of identifying processes of deduction with information transmission.

Furthermore, the methods used by Raven depended upon those developed by Dancoff and Quastler, yet they themselves stated that to measure complexity, 'the interrelationships of parts would have to be taken into account', admitting they would make no attempt to measure this. (S.M.Dancoff and H. Quastler (1953) [94].

See also 5.1.1 below, where we look at how systems theoretic thinking moved on from the application of Information Theory to problems of development, to the consideration of more elaborate processes involved in the development of organisation and complexity.

4.3.3 Patterns and their Representation as Networks, in the Modelling of Living Systems

The limitations of the Shannon-Weaver theory of information for theoretical purposes, when empirical work led to concepts of *genetic programs, genetic information and coding*, and *information transfer*, soon became apparent. (*See 4.3.1 and 4.3.2 above.*) Its shortcomings, however, instead directed attention

towards more elaborate and relevant concepts, such as *order*, *pattern*, and *complexity*.

The school of *organismic biology* played a key role in the origins of 'systems thinking' during the early 20th Century, to which we alluded at the start of this Chapter. It introduced and elaborated upon the idea that the essential properties of living systems are properties of the whole organism, and cannot be understood in terms of its parts alone. Such properties arise from interactions and relationships between the parts. It was Paul Weiss (e.g. in his *Within the Gates of Science and Beyond* (1971) [97], who made it his lifetime's endeavour to promote systems theoretic concepts (which stemmed from his earlier interests as an engineer) within the life sciences. The key concept, as expressed by Capra and Luisi, [82], p95, is that '... systemic properties ... arise from a configuration of ordered relationships. They are properties of a pattern [and] what is destroyed when a living organism is dissected is its pattern. The components are still there, but the configuration of relationships between them - the pattern - is destroyed, and thus the organism dies.'

It is worth noting here that systems theory stands in opposition to the method of *analytic thinking*, or *reductionism* promoted strongly, and with great influence in the Western world, by René Descartes. As Capra and Luisi also point out ([82], p66), 'The great shock of 20th Century science has been that living systems cannot be undersood by analysis. The properties of the parts are not *intrinsic* [to those parts], but can be understood only within the *context* of the larger whole.' They go on to say 'In the systems approach, the *properties of the parts* can be understood only from the *organisation of the whole*.'

The contribution that the cyberneticists brought to this debate was that they were neither biologists nor ecologists, but inclined to think more generally as mathematicians, engineers, neuroscientists and social scientists. As intimated above in 4.1, they were concerned with more abstract and generalised levels of description. (cf Ashby's distinction between the syntactic and semantic approaches to cybernetics, *pp64-5 above*.) This led them to their concepts of *feedback*, *self-regulation*, and then to ideas of *self-organisation*. A great contribution from Wiener was his appreciation that cybernetic ideas such as *signal, or message*, *control and feedback* actually made reference to nonmaterial elements (cf Thompson's message XII in Chapter 1) that are essential to meaningful description of life and living things.

As Capra and Luisi explain ([82], p87, '[The] attention to *patterns of organisation*, which was [only implicit] in organismic biology and Gestalt psychology, became the explicit focus of cybernetics.' [Wiener later] expanded the concept of pattern, from the patterns of communication and control that are common to animals and machines to the general idea of *pattern as a key characteristic of life.* They go on to quote one of Wiener's most poetic and perceptive passages - 'We are but whirlpools in a river of ever-flowing water. We are not stuff that abides, but patterns that perpetuate themselves.'

Thompson would have been proud to have come up with this statement, and may even have come to accept that his concept of *form* (see his message XI, pp13-15 above) could be usefully complemented by (if not generalised by, or made synonymous with) Wiener's concept of *pattern.*

Thus we meet with yet another *dichotomy* (see 2.1.3, p31 above), that of *analytical* versus *contextual* thinking. (Clearly this has much in common with the *reductionist* versus *holist* dichotomy, which we have already highlighted as an ambiguity in Thompson's thinking (e.g. see discussion on pp25-31 above.)

Thus, we have outlined the importance of *pattern*, and in particular *patterns of organisation*, in the understanding of living systems. In this regard, F.Capra, and P.L.Luisi, [82], p95, write : 'As the early systems thinkers discovered, the most important property of this pattern of organisation, common to all living systems, is that it is a *network pattern.* Whenever we encounter living systems - organisms, parts of organisms, or communities of organisms - we observe that their components are arranged in network fashion. Whenever we look at life, we look at networks.'

A significant property that soon emerges in the study of networks is their *nonlinearity.* In a network, a message, an influence, or some other form of communication, can travel along a cyclical path which may act as a feedback loop (***see 4.2.2 above***). Thus, the connections between the nodes of a network represent *nonlinear relationships.* It is feedback loops, underlying the formation of pattern in living networks, that bring about their capacity to *self-regulate.* This in turn can lead to the spontaneous ability of the living network to *self-organise* - ***see 4.4 below.*** Hence, the ability to self-organise in living networks arises from processes of communication and feedback.

The history of systems thinking, and of systems biology in particular as outlined above, leads us to the key concept in developmental biology of *self-organisation.*

4.4 Self-organisation

In the 1950's, physical analogues were constructed, of binary networks such as the *McCulloch and Pitts neural networks* - ***see 4.2.3, p69 above***. For instance in some, lights switching on and off represented the nodes. Given a randomly distributed initial configuration of lights, on or off (an *initial state* of the network), and a predetermined set of conditional decision procedures for switching lights on or off, then after a short period of random flickering, some *ordered patterns* would *emerge* in most such networks. These might take the form of waves of flickering lights, passing through the network, and/or repeated cycles.

These ordered patterns were seen to emerge spontaneously, and this *spontaneous emergence* became known as '*self-organisation*'. ***In Chapter 6***, we will discuss the modern mathematical approach, using *network theory*, to the study of such spontaneous emergence of patterns in networks.

Capra and Luisi ([82]), p94 *et seq*, consider the modern concept of self-organisation to have arisen during the 1970's, when the idea of *pattern of organisation* came to be a central focus in systems thinking, defined as 'a configuration of relationships characterising a particular system'.

The 'systems' viewpoint favoured the idea that 'The understanding of life begins with the understanding of *pattern*'. Echoing the idea of a non-decomposable system (***4.1 above***), the properties of a system (*systemic properties*), are properties of a pattern. e.g. if a living thing is dissected, whilst the component parts may still be recognisable, it is the structural and/or functional relationships between the parts that are lost.

Network models came to be linked to the development of new branches of finite state mathematics - *automata theory*, and *formal languages*. These, and their contribution to *developmental biology*, will be briefly considered in Chapter 5 below. *See also Chapter 6, Section 6.2.*

CHAPTER 5

Finite State Models of Development

A.M.Turing (1937, and 1938), [98] and [99] in order to tackle problems in the foundations of mathematics, devised a theoretical computer (now known as the *'Turing Machine'*), thereby originating the field of computer science. The machine is essentially a *deterministic automaton* whose action at a time **t** depends on a selection of possible pairings of one element from a finite set of *input symbols*, with one from a finite set of *internal states* at time **t-1**. As described by M.J.Apter, in Appendix 3 of [86], the machine comprises five components :

- an infinite linear tape divided into squares (hence the description *'infinite automaton'*);
- a finite set, **S**, of symbols which may be written singly, at a time **t**, inside these squares;
- a *read-write head* which can read whatever symbol is written in each square of the tape (only one of which lies under the head for reading at any time **t**). The head can replace the symbol by the same or another symbol from set **S**, and can then move the tape one square to the left, or one square right;
- a *controller* which can be in any one of a finite set of *internal states*, **Q**;
- a finite list of *conditional instructions*, **I**, showing for a certain subset of possible combinations of tape symbol and internal state, what should be the action of the read-write head. If no such matching of an instruction with a paired internal state and a tape

symbol is found in the list, the machine stops.

Representing internal states by **q**'s, tape symbols by **s**'s, and the instructions to move the tape left or right respectively as ← or →, then a particular Turing machine can be represented by a finite list of *instructions*, of such forms as :

$q_2\ s_1\ s_0\ q_5$,

which reads 'if the machine is in state q_2 and the head reads symbol s_1, then replace s_1 with s_0, and change the internal state to q_5', or

$q_4\ s_0 \rightarrow q_4$,

which reads 'if the machine is in state q_4 and the head reads s_0, then move the tape one square to the right, and leave the state unchanged.'

Each instruction is referred to as a *quadruple*, as it has four components. An automaton, in Turing terms, is defined by the set of quadruples comprising its instructions. The existence of a *'Universal Turing Machine'* which can carry out the computations performable by any other Turing machine, was proved by Turing himself.

Moreover, it is demonstrable (e.g. Stahl and Goheen (1963) [100] - as cited in Apter, [86], p.8) that in some cases, systems that are identical as far as input-output relations are concerned can be represented in terms of a network, as well as by a list of instructions. They give a Turing machine representation of a McCulloch and Pitts network (*see 4.2.3 above*), and in this case the network is simpler to conceptualise, and is more efficient in use, than the list of instructions.

5.1 Some Early Philosophical Difficulties

Before looking more explicitly at the use of finite state models of development, it helps to address some philosophical problems that led to misunderstandings in the early history of this aspect of developmental systems theory.

5.1.1 Preformation *versus* Epigenesis

These two concepts go back at least as far as Aristotle, and thus belong amongst the explanations of development in E.F.Keller's category of 'models without the help of genes' (***Chapter 3, p39 above***). They were the earliest attempts at answering the question 'How can the part contain the whole?' - see M.J.Apter [86], p52. Or, in more specific biological terms : given that the egg-cell (ovum) originates as a part of the adult organism, how can it give rise to the whole adult organism (through processes of replication and development) - complete with one egg-cell or more?

Of course the above use of reproductive terminology glosses over the case of sexual reproduction, and relates more exactly to forms of clonal reproduction, involving formation of zygotes without the need for male gametes - e.g. as in the processes of parthenogenesis in certain insects, or apomixis in pseudosexually reproducing plants such as brambles *Rubus fruticosus agg*, or dandelions *Taraxacum agg.* However, true sexual reproduction fits, to a first approximation, into the general scenario sketched out in the above problem, if we are concerned only with the organisational or functional features of an egg-cell or zygote, and not also with informational content, as conveyed in the genome.

The *preformationist* viewpoint posits the existence of *preformed* parts of the adult organism, and that ([86], p85) 'development is primarily a conversion of *latent* into *manifest* differences without an increase in the *complexity* of the organism, and without the *emergence* of new properties.' (Our emphases here highlight early usage which has carried forward into modern terminology, particularly that in the field of *complexity theory* - ***Chapter 6***).

The epigeneticist viewpoint claims that 'the organism starts from [a low level of] *organisation*, and that during development there is an increase in *complexity* and [the *emergence* of] quite new properties - [86], p85.

Referring back to 4.3.2, p72, question 3 above, it is interesting to contrast the beliefs of workers in this field at the time. Raven, for instance, explained that because the amount of *'specific information'* does not change during development, this led him to take a 'preformationist' view. Others believed the information content of the embryo must increase during development, and they thus favoured the 'epigeneticist' standpoint (e.g. W.M. Elsasser (1958) [101]). In light of their criticisms (***see 4.3.2, pp72-73 above***), Apter and Wolpert felt both standpoints 'failed to recognise that the problem of epigenesis and preformation deals essentially with the *development of organisation and complexity*', [86] p86, thus casting doubt on the idea that Information Theory might help elucidate the classical developmental dichotomy of preformation *versus* epigenesis.

It is important not to confuse use of the adjective ‘epigenetic’ in the sense of ‘pertaining to epigenesis’, with the modern use of the noun ‘epigenetics’, and its adjectival form ‘epigenetic’ - Section 3.4.

5.1.2 Self-reproduction *versus* Development

In the 1950’s the possibility of creating self-reproducing machines was a popular field of investigation, related to the rise of cybernetics and computer science. However, this work had perhaps more relevance to engineering applications, than to an understanding of development in biology. Much of this work was reviewed by Edward F. Moore (1961) [102], in the paper *‘Machine models of self-reproduction’*, presented at a Symposium on Mathematical Problems in the Biological Sciences. Most of the models, including hardware demonstrations, were not particularly mathematical in nature. However, John von Neumann, in following up Alan Turing’s work on automata, instigated much of this work - e.g. John von Neumann (1951) [103].

The philosophical problem at the heart of these studies was that of self-reference. Apter [86], p.155 describes this as follows: ‘the [self-reproducing] automaton must not only be able to completely specify what it can do, but it must be able to specify how it specified itself, or describe the part of it which is describing itself. [Otherwise] we go into ... an *infinite regress.* So at some stage or another there must be complete self-reference by one of the parts of the system to itself.’ Lester G. Barth (1953) [104] translated this into explicit biochemical terms, by noting ‘if every reaction in a cell requires an enzyme, and enzymes are produced only by cell reactions, then there will be an infinite regress unless sooner or later a reaction is *self-catalysing*, i.e. it produces an enzyme which catalyzes [the reaction] itself’.

von Neumann’s approach to self-reproduction, 1951, was an extension of Turing’s work on infinite automata, to show that such an automaton could be self-reproducing. In essence, such an automaton is constructed as follows :

- Input the description of a machine **A** into a universal Turing machine (or universal automaton), **B**; [1]

- Then let the *behaviour* of machine **A** be the output of **B**;

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[1] In this context, von Neumann used the term ‘*universal constructor*’. In Turing machine terms, a reservoir of machine parts substitues for the tape.

- Suppose the output of **B** (i.e. the behaviour of **A**) to be, not an output tape, but a sequence of instructions for building a machine **C**;

- Let machine **C** be a universal automaton identical to **B**;

- Then universal automaton **B** produces a copy of itself.

More briefly, the input of **B** is a description of **A**, which builds machine **C**, which is identical to **B**.

Apter, [86], p62 remarks that the credibility of an automaton output resulting in the building of another machine is 'not a theoretical but a practical difficulty. ... one could imagine the universal automaton sitting on a reservoir of standard machine parts which had to be fitted together in an ordered sequence. In Turing machine terms, the tape is substituted for machine parts.'

Clearly this theoretical model has little relevance to biological development, which is distinct from, but may be considered to include, self-reproduction. There is also a sense in which development can be part of the ultimate objective of self-reproduction, at least in multicellular organisms. Reproduction of an organism, plant or animal, is usually accomplished through a smaller, apparently simpler intermediary such as a seed, spore, or fertilised egg (zygote). The process must necessarily be *internally controlled.* However in the von Neumann model, the process of 'development' is more a process of *growth* (or maybe better, *assembly*), and is *externally controlled* by the machine which is doing the assembling. 'That is, the first machine is making the second machine, [rather than] the second machine making itself under instructions given to it by the first machine.' (Apter, [86], p64.)

5.1.3 The Interrelationships of Parts, and the Significance of Connectedness in Developmental Modelling

In a personal communication to M.J.Apter (cited, [86] p65), Lewis Wolpert asked '... why is it easier to build a toy paper bird from an ordered set of instructions on how to fold paper than it is from a direct examination of the finished product? [Yet] a painting would seem to be easier to reproduce from the finished product than from a set of verbal instructions.'

The speculation was that, whereas the painting can be viewed as a whole (*holistically*), with no interdependence of parts, the paper bird involves interdependence of parts, and the folding has to be performed in a particular temporal sequence.

Wolpert's question touches upon the differences between reproduction by copying, characterised (e.g. by G. Gamow *et al* (1956) [105], as the *cryptographic approach*, as opposed to *deductive* and/or *programmatic approaches*, ***to be discussed further below (5.3.1)***.

Gamow was considering the problem of protein synthesis through the agency of DNA and RNA nucleotide sequences as *templates* for amino acid sequences. Thus, it is clear that life uses *replication by template* (J.D.Watson and F.H.C.Crick, 1953 [79]), thereby circumventing the 'infinite regression' problem ***raised in 5.1.2 above***. However, in the broader context of development, we also meet processes best modelled by *programs* or *grammars* and, related to the latter in particular, by *networks.*

Replication by template, but at the level of the entire germ cell (A.Weissman (1885) [106]), gives a paradigm shift in how reproduction and development of whole organisms is viewed. Traditionally the adult is considered to reproduce itself through the intermediary of the germ cell. (For simplicity, the complications introduced by the mechanisms of meiotic recombination and fusion of gametes in sexual reproduction, enhancing genetic and consequently phenotypic variability, are set aside here). The idea that germ cells self-reproduce in template fashion, with the potential to develop into the more complex adult form, makes the whole process of development an agency for the self-reproduction of germ cells.

This helps answer the question as to why organisms develop at all, and why they do not merely self-reproduce directly, following the von Neumann model (***5.1.2 above***). Self-reproduction of the germ cell in template fashion can, from the Weissmann viewpoint, have as a 'side-effect' the potential of its development into a larger and more complex representation of itself - the adult organism. This must have much to do with the evolutionary *selective advantage* accruing from *multicellularity.* It also makes possible the development of *levels of complexity* unachievable through replication by template alone.

Some Types of Interconnectedness Involved in Development T.Gustafson and L.Wolpert, in the early 1960's (e.g.(1961) [107]) stimulated interest in the role of physical forces in shaping the embryo during development. This contributed a significant counterpoint to the concurrent emphasis on *molecular genetics* and how genes interact in developmental processes (***3.4 and 3.5 above***).

Their focus was on the 'forces which shape the embryo', and this was in a way a revival of one of the key messages from D.W.Thompson - *see message X, pp9-11*. Thirteen of the seventeen chapters in his book principally concern the

role of ‘physical laws and mechanisms’, including physical forces. He believed them to be among the most significant factors in determining the form, and changes in form, of the developing embryo on all scales, from the internal structure of the cell, up to the whole organism.

Even in 1917, Thompson and contemporaries realised that such interactions must occur at all levels - e.g. from those between molecules, between the nucleus and cytoplasm, between cells, and between regions of the embryo.

Gustafson and Wolpert highlighted the central importance of the *interconnectedness* of the parts of a developing system, in that one particular change or event can result in many other changes throughout the system.

They gave several examples to illustrate this: e.g.

- consider a single layer of cells arranged in a ring, each cell in contact with one neighbour on each side. Then if there is a change in *adhesion* between all cells in contact in the ring, this single change in the property of *mechanical connectedness* will affect the shape of all cells in the ring, and probably the dimensions of the ring; or:

- consider a sheet of cells all attached to an underlying planar membrane, then if the cells all increase their area of contact with their neighbouring cells, while maintaining their contact with the membrane, the morphological effect will be to cause the cellular sheet to curve.

Some important general conclusions from such examples are that :

- just a single change in a property, such as intercellular adhesion, can spawn a range of other events, which would be more complicated to describe in their entirety than would the single causative change. Of course, the latter might itself be determined by the switching on or off of a gene, or some other gene regulatory process;

- *a propos* ***the discussion in 4.3.2*** , it is not meaningful to ask whether there is a change in information content in the system before and after the causative event;

- moreover, there seems no way that such changes could be labelled as ‘preformed’ or ‘epigenetic’.

Apter suggested resolving this syntactic dilemma by use of the term ‘*preformed epigenesis*’ for such processes. ‘That is, the original action was predetermined, but the mechanical results were of a [qualitatively] different nature, ... and

were not as such described [or anticipated in any way] in the instructions'. ([86], p163)

On such arguments, Apter and Wolpert concluded, [86], p87, that '... information theory has little bearing on events such as those described, and an [attempted] analysis in terms of preformation and epigenesis shows the complete inadequacy of such concepts'. Also, '... the question is essentially that of how development should be *described* rather than of its real nature : that is, that it is a semantic rather than an essentially empirical problem'.

In a strange way, their argument takes us back full-circle to the descriptive approach of D.W.Thompson. The difference is that, as Thompson admitted, his approach was insufficient in lacking any unifying explanatory principles. Apter and Wolpert, however, could advocate a descriptive approach, knowing that it could now be backed up by such underlying principles.

In the rest of this Chapter, we consider two ways in which finite state theories have been developed to model more effectively processes of development rather than just self-reproduction - these are *automata nets*, and *Lindenmayer systems/languages.*

5.2 Growing Automata Nets

M.J.Apter[86], Ch. 6, p112, discusses these in the context of the question 'How can a complex organism develop out of instructions to only one single unit, the original unit (zygote, fertilised egg, seed) of the organism?'. To make this question more precise for the purposes of such entirely theoretical models as automata nets, he restricts the idea of development to the notion of *spatial differentiation*. To clarify the significance of this, we need first to consider some of the terminology of developmental biology in a little more detail.

5.2.1 Growth *versus* Development

Despite widespread confusion in the early literature, it is now generally agreed that *growth* implies increase in size only, while *development* includes growth, but can include all other changes which occur during the tansitional stages from zygote (or other specified starting unit) to the adult form. Most significant among these other changes are the processes implied by the term '*differentiation*'.

The distinction between growth and differentiation was well summed up by P.Weiss (1949) [12] : "If 'growth' means more of a kind, 'differentiation' means more kinds."

Both growth and differentiation may occur alone in a developing organism, but certainly in the long-term during development, they will occur together. Of course 'growth' can, from case to case, be defined and/or measured differently : e.g. increase in spatial dimensions, mass, number of cells, or in some metabolic constituent. This in turn means there can be many ways of defining differentiation. Moreover, there are many ways in which a system may differentiate, which are independent of one another. Hence, many taxonomies have been devised to distinguish types of differentiation, and one of the most useful is that of C.H.Waddington ([13], and [76]), which recognises four basic types. Paraphrasing from M.J.Apter, ([86], p38) :

Histogenesis - changes in the chemical makeup and/or activity within a body of living material;

Regionalisation - an increase in the number of distinctive functional, and/or anatomical/morphological regions within a developing embryo;

Morphogenesis - the physical moulding of a mass of living tissue into a structure with coherence, and a characteristic form;

Pattern Formation - the emergence of distinguishable parts organised with characteristic geometrical/spatial relations.

Waddington also distinguishes histogenesis from regionalisation by stating, '[The latter] shows a difference between two *spatially distinct but contemporaneous entities*, while the former shows a difference between two *temporal states of the same entity*.'

The idea of pattern formation has been elaborated in current usage to refer to the *spatial organisation* of the whole organism, and as Apter [86], pp38/9 points out, this notion in turn distinguishes two kinds of differentiation :

Functional Differentiation - includes regionalisation in Waddington's sense above, but maybe also the labelling of individual cells as a preliminary to possible regionalisation. (This concerns the emergence of different ways in which cells may behave, and relates also to the determination of *cell fates*, in embryological terms);

Spatial Differentiation - this refers to changes in the geometry (*spatial organisation*) and/or in the topology (*patterns of connectedness*) across the developing organism.

Of course both types of differentiation could, and commonly are, encountered simultaneously, though in general there is not necessarily any relationship between them.

So for now, having delimited our area of application of automata nets to the phenomena of spatial differentiation, let us characterise what is meant by a *growing net automaton*, and give some examples.

5.2.2 Constructing Growing Net Automata, with Examples

Returning to Apter's question (***5.2 above***), about the problem of development ([86], p112), the above restriction yields a more precisely phrased question: 'How can spatial differentiation occur during the process of continual self-reproduction of an original set of instructions and with no external interference?'

Clearly, the motivating idea underlying this question is that we consider the developing organism, starting with the single cell zygote, to grow and differentiate by the repeated reproduction of cells, along with their changes in form and function towards some set of *terminal states*, corresponding to a range of *tissue types*. The cells in the real, living network are therefore to be modelled by the automata in the net.

An *automata net* comprises a set of automata, each of which can communicate directly with at least one other automaton in the net. In Turing terms, each automaton can be treated as a Turing machine in its own right. (***See pp77-78 above***.) However, there are no instructions for moving the tape in these (simplified) automata. Instead, the tape is constrained to move in one direction only, one square at a time, at each discrete time step. The tape movements across the network as a whole are required to be *synchronous*.

However, should an automaton reach a terminal state (i.e. a state $\mathbf{q}$ for which there is no instruction), then the tape stops for this automaton.

The tape is the only channel of communication available between automata in the net. Unless otherwise stated, a tape square contains one or other binary digit, 1 or 0 - i.e. the set of tape symbols, $\mathbf{S} = \{0, 1\}$. When, at any time step, an automaton is in communication with more than one other automaton, it sends the same binary symbol to every automaton with which it is linked. [2]

Related to our discussion in 5.1.2 above, there is one possible output of an automaton other than a tape symbol - i.e. an identical (*self-reproduced*) automaton. In Turing terms this means a Turing machine with the same instruction set as its ‘parental’ automaton. This output is represented by the symbol **R** (*Reproduce*). This circumvents the problem discussed above that, logically, self-reproduction is a necessary perequisite of development. When the output is **R**, a new automaton is produced, possessing the identical instruction set to that of its progenitor, complete with an input-output tape loop.

In what follows, by convention, each newly generated automaton starts in state q_1. The output of each automaton (except for **R**) is the input, at the next time step, to all the automata it has created through the output **R**, and to its *progenitor* (direct ‘ancestor’).

Thus, the above construction is designed to generate an *automata net*, which grows from an original automaton, whose instruction set includes the instruction to reproduce itself. It is intended to demonstrate *spatial differentiation* (***5.2.1 above***), during the self-reproduction of an original set of instructions.

A limited range of examples is presented below, but should the reader wish to see more elaborate models, Chapter 6 of M.J.Apter [86] gives more comprehensive coverage, and highlights the technical complications that have to be introduced to cope with higher levels of complexity.

One such technical issue to be addressed straight away is that, because Turing instructions are *conditional* (dependent on the presence of an input), it is assumed that the input to the original automaton of the net is always a 1 at each timestep. So a continual s_1 input is arbitrarily chosen to activate this automaton at all times. It appears in the following examples as the s_1 to the right of the q representing the original automaton.

5.2.3 Simple Examples of Developmental Algorithms

To illustrate the use of such models, we ask the question ‘Given a specified spatial pattern, can we choose a set of instructions to an original automaton, which will generate this pattern?’

Example 1 Consider the simplest possible pattern - a straight line of automata. Unlimited growth in a straight line, ***using the notation on pp77-8 above***, can be generated if the starting automaton has the following instructions :

---

[2] By assumption, a tape square is understood to pass from one automaton to its neighbour(s) in the net, at each time step.

$q_1\ s_1\ \boldsymbol{R}\ q_2$

$q_2\ s_1\ s_1\ q_2$

The following gives the sequence of *instantaneous descriptions* of the automata net as it grows. (The symbol $\prec$ serves to separate the successive instantaneous descriptions of the growing net.) In these descriptions, the limitless supply of s_1's to the original automaton alluded to above, is simply represented by the one s_1 being read by the head at that time step - i.e. the s_1 just to the right of the current internal state symbol, q, of that starting automaton :

$q_1\ s_1 \prec q_1\ q_2\ s_1 \prec q_1\ s_1\ q_2\ s_1 \prec q_1\ q_2\ s_1\ q_2\ s_1 \prec q_1\ s_1\ q_2\ s_1\ q_2\ s_1 \prec$

$q_1\ q_2\ s_1\ q_2\ s_1\ q_2\ s_1 \prec$ .... , etc. (No terminal net.)

Example 2 Self-limiting growth - to produce a line just two automata long, the following instruction set can be used:

$q_1\ s_1\ \boldsymbol{R}\ q_2$

$q_1\ s_0\ s\ q_3$

$q_2\ s_1\ s_0\ q_3$

The sequence of instantaneous descriptions is :

$q_1\ s_1 \prec q_1\ q_2\ s_1 \prec q_1\ s_0 q_3\ s_1 \prec s\ q_3 q_3\ s_1$

This is terminal, as there is no instruction for state q_3. The unsubscripted 's' means that the value of the tape symbol, 0 or 1, is immaterial.

Example 3 It is an easy matter to generalise such self-limiting growth to any specified number of automata. e.g. for a line of three automata, the instructions are :

$q_1\ s_1\ \boldsymbol{R}\ q_2$

$q_1\ s_0\ s\ q_4$

$q_2\ s_1\ s_1\ q_3$

$q_2\ s_0\ s_0\ q_4$

$q_3\ s_1\ s_0\ q_4$

The sequence of instantaneous descriptions is :

$q_1\ s_1 \prec q_1\ q_2\ s_1 \prec q_1\ s_1\ q_3\ s_1 \prec q_1\ q_2\ s_0\ q_4\ s_1 \prec q_1\ s_0\ q_4\ q_4\ s_1 \prec s\ q_4\ q_4\ q_4\ s_1$

This is terminal (no instruction for q_4).

In general, for a required length, n, of automata in the terminal line, it can be shown by induction on n that an input of s_1 results in a reproduction, and an s_0 in the automaton entering its final state (with the exception of the starting automaton, which changes states until a programmed state is reached at which its output changes from s_1 to s_0). Then N = n, where N is the number of time steps needed to derive the terminal descriptiion of the net.

Example 4 The above are all examples of growth rather than true development involving spatial differentiation, but they illustrate well the basic principles of this type of modelling. C.J.Apter, [86], Ch.6 gives many more examples, some demonstrating spatial differentiation. ***Fig.5.2.1*** is based on one of these, producing a Y-pattern comprising five automata, one central automaton being connected to the other four, which can only communicate with one another through the central automaton.

Further notational conventions are introduced, as used in the figure. e.g. if there are multiple inputs to an automaton at a given time step, then the simultaneous inputs are placed in a bracket as follows : $q_1(s_1\ q_0)$. The arrow symbol $\uparrow$ is used for symbols on a *return loop*, and refers only to the symbol to which it is adjacent. (For simplicity, the arrow is not included in instantaneous descriptions where the original automaton contains no quadruples for dealing with simultaneous inputs.)

Apter comments that '[In such models], in contrast to the straight line cases, *feedback* ... [becomes] essential to the process. Indeed, we have here a simple model of *synergistic induction*, for mutual interaction between automata causes each ... to act in a way that it would not have done otherwise.'

Moreover, such models are counter to the view that, in order to explain differentiation, we must assume that instructions must be lost during differentiation (e.g. A.Weismann (1955) [106], pp210-14. As Apter describes very well, 'In these models there is no *static "structural" change* in the instructions : different parts of the instructions simply become viable at different stages in a *dynamic interacting system.* And the growth is *internally controlled* through the fact that the same instructions have different results at different stages due to the altering pattern of the development itself. That is, the "organism" that is being produced is a dynamic one which itself affects its own growth behaviour, different properties being called forth at different stages by the "organism" itself.' (*Italics* and "double-quotes" here are my own.)

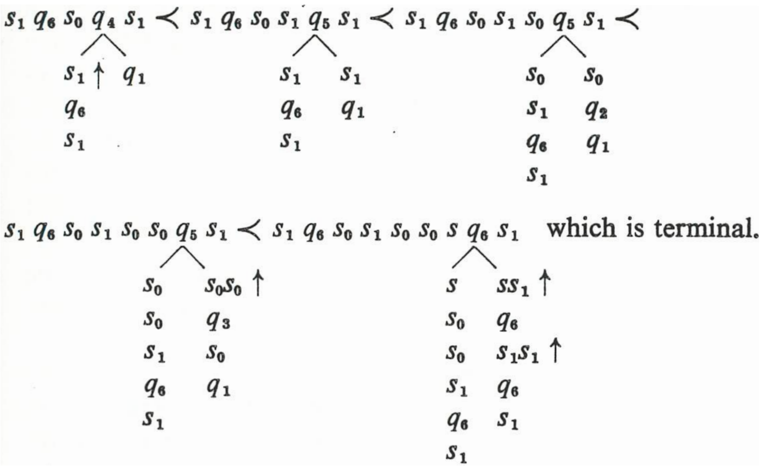

Figure 5.2.1: How a Y-pattern can be produced: this figure shows the final 5 instantaneous descriptions from the 11-instruction set listed in the text. The whole derivation requires 9 steps. Adapted from pp118-9 of M.J.Apter, p118 [86]

The five instantaneous descriptions in ***Figure 5.2.1*** are the final steps in a derivation, starting with the following instruction set:

$q_1\ s_1\ \boldsymbol{R}\ q_2$

$q_1\ s_0\ s_1\ q_6$

$q_2\ s_1\ s_0\ q_3$

$q_2\ s_0\ s_0\ q_3$

$q_3\ s_1\ \boldsymbol{R}\ q_3$

$q_3\ s_0\ s_1\ q_6$

$q_3\ (s_1 s_1)\ s_0\ q_4$

$q_4\ s_1\ \boldsymbol{R}\ q_4$

$q_4\ (s_1 s_1)\ s_1\ q_5$

$q_5\ s_1\ s_0\ q_5$

$q_5\ (s_1 s_0)\ s\ q_6$

The great disadvantage of growing automata nets is that the number of instructions needed tends to be large. In the straight line examples above, the

smallest number of instructions necessary to produce a line of n automata was 2n - 1, requiring 2n - 1 time intervals, and automata in n + 1 distinct internal states. However, net automata, being based upon Turing machines, are concerned more with generality, than with the need for speed and efficiency. It is the latter which is the main consideration in the more realistic models of biological systems, or in engineering applications.

With this in mind we next turn to an alternative class of finite state developmental models based, not on automata, but on the related theory of *Formal Languages*. We briefly consider *Lindenmayer Systems and Languages*, and *Genetic Grammars*.

5.3 Lindenmayer Systems, Lindenmayer Languages, and Genetic Grammars

This subject area was exhaustively covered (in its history up to 1975) by G.T.Herman and G.Rozenberg (1975) [108]. This book covers the formal theory of *developmental languages* and *sequences*, along with less formal discussion on more biologically motivated topics.

In his introductory chapter to the book, Aristid Lindenmayer (who originated this topic, soon to become known as *Lindenmayer Systems*, or *L-systems*) said that these mathematical constructs 'grew out of an attempt to describe the development of multicellular organisms in a manner which takes genetic, cytological and physiological observations into account in addition to purely morphological ones.' He developed the theory in a series of publications between 1964 and 1973. (e.g. A. Lindenmayer (1968) [109] and [110]; and (1971) [111].)

More recent work is reviewed in a collection of papers, *Lindenmayer Systems (1992), Eds. G. Rozenberg and A.Salomaa* [112]. In their Preface they highlight that '[Lindenmayer] was convinced that for many biological phenomena [such as growth and development in plants], relational and set theoretic concepts were more suitable than mathematical analysis. The discrete and combinatorial nature of biological structures, from the molecular to the cellular and population scales was obvious to him.'

Instead of arrays of finite state automata (***5.2 above***), models from *formal language theory* proved to be more economical and efficient, especially for computer implementation.

5.3.1 How L-systems Relate to Chapters 2 , 3 and 4 above

L-systems theory addresses many of the themes discussed in our story so far. This is well demonstrated in [112] in the paper by A. Lindenmayer and H. Jurgensen, *Grammars of Development: Discrete-State Models for Growth, Differentiation, and Gene Expression in Modular Organisms.*

They point out that 'severe abstractions' are needed to discuss development in terms of *gene expression* and *molecular mechanisms of differentiation*, due to the complex and combinatorial nature of what is to be described.

L-systems arose from the abstraction of a *developmental program* (or perhaps a better term is *developmental grammar*) to provide a framework within which all aspects of the empirical observations could be organised.

Paraphrasing from [112], p4: 'The fact that all cellular components must eventually be coded in DNA does not mean that all cellular processes are under its direct control. [e.g.] membrane properties like *polarity* are propagated from cell to cell without DNA involvement. In general, spatial aspects of development often cannnot be directed by on-off states of genes : they have to be specified by pre-existing cytoplasmic [or cell wall or membrane] structures. On the other hand, it is difficult to underestimate the role which genes play in development. We take into account both the *"genetic"* and the *"structural"* control elements in our [L-system] models.' [The "double-quotes" I have placed within this quotation appear as single quotes in the original. All other emphases here are my own.]

It is worth comparing the above with the observation of D.W.Thompson in OGF(1), pp154-5 - concerning 'the beginning of morphological', as opposed to 'the end of physiological enquiry' (*see 2.2, p34 above*). The modern view, as exemplified by L-systems theory, recognises the need to integrate our knowledge of the fabric and functioning of life, with the more descriptive aspects of 'morphological enquiry'.

Lindenmayer and Jurgensen go on to ask if it is better to speak of a *'program'* or a *'grammar'* in the modelling of multicellular development from zygote to adult.

A program implies a set of rules to be executed, and these must be applied to many different cells or groups of cells (maybe clones) simultaneously in the developing organism.

A grammar is also a set of rules, but it specifies substitutions of subunits of a structure, by other subunits or groups of subunits.

They argue that 'because of the distributed character of multicellular development, a "grammar" may be more applicable than a "program".' In support of this, they cite Gunther Stent (1982) [113] : '[a programmatic phenomenon requires that] in addition to the phenomenon itself, there exists a second thing, the "program", whose structure is isomorphic with, that is, can be brought into one-to-one correspondence with, the phenomenon. [Considering development,] it is most unlikely that the overall sequence of events is isomorphic with the genome'.

5.3.2 Some General Aspects of Formal Languages

In applying *Formal Language Theory* to developmental problems, the *words* will correspond to the biological structures, and the *letters* to the biological subunits. A *grammar* specifies the possible *transitions* from a given word to some other word(s) by replacement of one or more of the letters by a single letter, a group of letters, or by *erasing* letters.

Grammars have been defined for structures other than just strings of letters - e.g. for *arrays*, *graphs or networks*, and *maps*.

L-systems are grammar-like constructs defined to provide descriptions of development. (This is not necessarily restricted to biological development - e.g. L-systems are well known for their applications in computer graphics - P.Prusinkiewicz (1990) [114].)

5.3.3 Construction of L-Systems as 'Grammars for Development'

Adapting statements in [112], p5, the biological reality to be modelled is as follows:

1 As cells divide, active genes in both daughter cells may be identical to those in the mother cell, or they may differ between the two daughter cells and/or the mother cell;

2 Changes in gene expression may be brought about by the activity of other genes in the same cell, or by the chemical agency of *inducers* or *inhibitors* produced by other cells (***cf 3.5, pp58-60 above***);

3 This distinction implies a basic *dichotomy of developmental control* - the control of gene expression through *cell lineages* on the one hand, *versus* control by *cell interactions.*

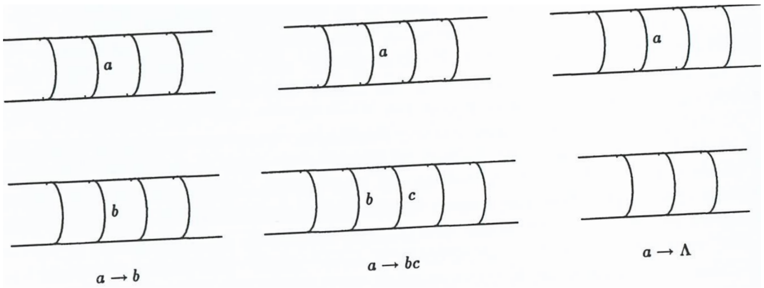

Figure 5.3.1: An L-system, showing three state transitions and their transition rules. Based on Fig.1, p6 of G.Rozenberg *et al* [112]

This dichotomy has to be reflected in the way the various elements of an L-system are to be defined.

We illustrate some general principles by considering the simplest class of L-system - those used to model the development of one-dimensional filaments of cells, as found in filamentous algae.

These are called *string 0L-systems.* The 'string' refers to a sequence of cell states, as shown in ***Fig.5.3.1***, and '0L' indicates an L-system with *zero-sided interactions.* i.e there is no interaction between cells from either side, and so 0L-systems model the cell lineage aspect only, of the dichotomy alluded to above.

A 0L-system S_1, is constructed from :

1 A finite set Σ of *symbols*, the *alphabet* of S_1, representing *cell states*

2 A finite set P of *state transition rules* (or *productions*) of the form $a \to \omega$ where $a \in \Sigma$, and $\omega \in \Sigma^*$ (the set of all strings of elements $a \in \Sigma$), and where a *rule* $a \to \omega$ represents the *transition* of cell state a, into the string $\omega \in \Sigma^*$

3 Inclusion of the *empty string*, Λ in Σ^*

4 Simultaneous application of the transition rules to each cell in the developing string in a succession of time intervals (or *derivation steps*). Actual choice of time interval will reflect time scales appropriate to the real system being modelled.

Thus, state transition rules can allow a cell to remain unchanged in its state, to change to another state, to divide into a string of cells each with a specified state and in a specified order, or to be *erased* from the string. (***See Fig.5.3.1 above.***)

Development starts with a *starting string* (or *axiom*), α, and a *derivation* from any string ω entails replacing each occurrence in ω of a particular symbol $a \in \Sigma$ by the string generated according to the corresponding transition rule. The derived substrings are concatenated as they are generated, in the order corresponding to the locations of their respective parental cells. (***See Fig.5.3.1 above.***)

A *derivation* may consist of any number of consecutive derivation steps, and L-systems can be constructed to be *terminating* or *nonterminating.* These can be thought of as possible *global properties* of the entire system, in contrast to the transition rules, which are *local properties*, applying at the level of individual cells (or *state symbols*).

If there is a single transition rule for each state symbol, then at each transition step, the string produced is unique. In such cases the the system is called a *deterministic 0L-system* or *D0L-system.* Systems can be constructed which are *nondeterministic* by allowing for different sets of transition rules for a given symbol or subset of symbols to apply at specified derivation steps. The choice of selection may be predetermined, or made by some stochastic process. Such L-systems are termed *table 0L-systems* (*T0L-systems*). This is because each set of production rules can conveniently be represented in table form.

Another expression of global behaviour is the set of all strings which could be produced by a given L-system - such a set is called the *language* of the L-system. Choice of terminology reflects the analogous constructs used in formal language theory.

5.3.4 Generalising the Applicability of L-systems

Of course the 0L-system ‘zero-sided’ restriction limits applicability to filamentous organisms, showing no cellular interaction. The Lindenmayer and Jurgensen article in [112] gives some examples of notational devices which can allow for the modelling of the growth and development of branching structures, or of patterns of cell polarity within a filament. Use of different types of bracketing (e.g. by indexing the brackets) can enable the marginal and/or interstitial growth of leaf-like structures, or the growth of certain solid structures, to be modelled.

Herman and Rozenberg, in [108], give examples of *L-systems with interaction* (*IL-systems*), modelling 1-sided or 2-sided interactions within a filament. The generalised taxonomy for these uses the notation $< k, l >$system, for natural numbers k and l. For a specified cell state, the cell in question is deemed to interact with k cells to its left, and l cells to its right. Thus a 0L-system could be written as a $< 0, 0 >$system in this notation.

The big limitation of L-systems in general remains their ready applicability almost exclusively to plant development, as the movement of cells or tissues relative to one another, as is common in animal embryological development, cannot readily be accommodated.

Before leaving L-systems it is worth noting that they differ from mathematically defined grammars in the sense of *Chomsky grammars* in two important respects :

- all subunits are transformed simultaneously in a structure at each derivation step;

- there is no distinction between terminal and nonterminal strings.

L-systems thus raised new questions in formal language theory, and led to new insights into language generating mechanisms, as well as in biological development.

5.3.5 Cellular Automata

Cellular automata (CAs) offer another style of simulation, with earlier origins than L-systems. They have remained more current, due largely to their adoption by S. Wolfram as a means of modelling physical and biological systems. He gave a thorough account of CAs in his very large book *A New Kind of Science* (2002) [115]. Wolfram argues that the greatest significance of CAs is their focus on 'how [their] parts act together to produce the complexity of the whole rather than on the constituent parts of the system.'

Their essential features are:

- In CAs, all variables (space, time, and dynamical) are assumed discrete. An abstract space is represented as a lattice (or *cellular automaton*) with a finite state machine located at each node.

- Each such machine evolves in time, by reading the states of the neighbours to which it is connected at time t_n and, according to simple, pre-specified and uniform rules, moves to a new state at time t_{n+1} .

It was von Neumann who first proposed that the simple dynamics resulting from such simple rules might bear a formal resemblance to the biological processes of self-reproduction and evolution. With this in mind, the idea was elaborated by allowing the strength of the interactions between elements to be progressively modified according to the effectiveness of the network in performing particular pre-set tasks. This was applied to develop *neural nets*, modelling networks of nerve cells, a particular example of a broader class of models termed *adaptive networks.* (***See 6.4.3 below, for an account of some recent work on these.***)

Lindenmayer systems have similarly been made 'adaptive' in this way - essentially the elaboration of the earlier formal description of the development of simple multicellular embryonic networks according to an evolvable set of rules, for such processes as *subdivision, reconnection, and modularisation.* (See E.F.Keller, (2009), p281 [48].)

For more on Cellular Automata, see 7.3.2 below.

In Chapter 6 below, on Complexity Theory and Complex Networks, we bring together much of the conceptualising which is discussed in Chapters 2 to 5 above. **Much of the theorising that has gone before was conceived in the pre-computational era, and the models considered would, in many instances, have lent themselves to hand calculations.**

With the advent of high speed computation, the possibility has arisen of investigating developmental systems in all their complexity. The examples to follow illustrate in particular, the use of complex networks as a basis for modelling.

CHAPTER 6

Complexity Theory and Complex Networks

In many places in his book *On Growth and Form* , [2] and [3], D.W.Thompson uses the terms ‘complex’, or ‘complexity’ in order to discuss the processes of growth and development. In 1917, these words were used in their colloquial, intuitive sense, before acquiring their more technical, though still not necessarily well-defined, meaning in the lexicon of modern *Complexity Science*. However, in places the germ of the modern meaning of complexity can be inferred in what he says.

e.g. in OGF(2), in introducing Huxley’s concept of *heterogony* ([3] p206), ***see 2.3 above***, we find ‘An organism is so *complex* a thing, and growth so *complex* a phenomenon, that for growth to be so uniform and constant in all the parts as to keep the whole shape unchanged would indeed be an unlikely and an unusual circumstance. Rates vary, proportions change, and the whole configuration alters accordingly.’

On p53 of OGF(1) ([2]) he sums up his lengthy discussion of the nature of forces shaping the developing embryo as follows : ‘... we may lay down the following general statements. The form of organisms is a phenomenon to be referred in part to the direct action of *molecular forces*, in [larger][1] part due to a more *complex* and slower process, indirectly resulting from chemical, osmotic and other forces, by which material is introduced into the organism, and transferred from one part of it to another. It is this latter *complex phenomenon* which we usually speak of as “*growth*”. [Thompson’s own “double quotes”.]

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[1] Thompson inserts the word ‘larger’ in the corresponding passage, p82 of OGF(2) [3].

He then develops this idea further in [2], p54, by characterising *'development'* as opposed to *'growth'*. In the following two paragraphs, Thompson implies 'complex' by reference to its converse, 'simple' - the emphases, both *italics* and "double quotes" below, are Thompson's own. Although an equivalent passage appears, p54 of OGF(1) [2], the wording is improved in OGF(2) [3], p82, the version on which this quotation is based:

'Every growing organism and every part [thereof] has its own specific rate of growth, referred to [this or that] particular direction; and it is by the ratio between these rates in different directions that we must account for the external forms of all save certain minute organisms. This ratio may sometimes be of a *simple* kind, as when it results in the mathematically definable outline of a shell, or the smooth curve of the margin of a leaf. ... [On the other hand] it may sometimes be a very *constant* ratio, in which case the organism while growing in bulk suffers little or no perceptible change in form; but such constancy[2] seldom endures ... , and when the ratios tend to alter, then we have the phenomenon of morphological "*development*", or steady and persistent alteration in form.'

C.H.Waddington ([13], pp284/5), in struggling with the lack of any single precise definition of growth, cited the following long passage from Weiss (1949) [12] as an illustration of the (in Waddington's own words) '*complexity*' involved even in the growth of a single organ : 'The original eye vesicle consists of a certain initial allotment of cells from the embryonic brain wall. At first, all of these cells divide. *The growth function at this stage is therefore a volume function.* In the cup stage the retina becomes multilayered, with a sharp division into a germinal and a sterile zone. Only the cell layer in contact with the outer surface, corresponding to the ventricular ... layer of the brain, continues to proliferate, while the cells released into deeper layers differentiate the various retinal strata without further multiplication. *The source of growth has thus become reduced to a 2-dimensional one, causing a marked decline in the relative growth rate taken over the whole organ (e.g. from measurements of diameter).* Later, the cells of the germinal layer themselves cease to proliferate and transform into sensory cells, a process which starts from the centre (*macula*) and spreads rapidly toward the periphery ... of the retina. Eventually only the cells at the rim retain residual capacity to multiply. Further growth is then essentially by apposition from this rim; that is *the growth source has shrunk from planar to linear extension.* Meanwhile, some of the neuroblasts, though no longer multiplying, grow in size as they sprout nerve processes, which, grouped into plexiform layers, add to the thickness of the retina. [A 'plexus' is a structure in the form of a network, formed by nerve fibres in this case.] During the latter stages a gelatinous secretion, supposed to come from cells of both the retina and lens, fills the interior with vitreous humour, thereby progressively distending the eyeball. In addition, blood vessels and other mesenchyme penetrate into

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[2] It may be significant that Thompson replaces 'equilibrium' by 'constancy' here, in amending the original OGF(1) [2] wording.

the eye from the surroundings.

‘This diversity and *complexity* of the component processes contributing to eye size makes the search for a single “*growth-controlling*” principle [Weiss’s own “double quotes”] appear utterly unrealistic ... .’

In what follows in this Chapter we examine how, for purposes of mathematical modelling, the technical definition of complexity has been made more precise than the colloquial use of the word. The concept of complexity to be considered below, relates to a class of developmental systems more restricted in scope than perhaps Thompson, Waddington, and Weiss had in mind. The example of the developing eye should in this modern context be thought of as a *complicated* system or process rather than a complex one. Complex subsystems or processes might possibly be found embedded within the overall (complicated) one, and such subsystems could possibly lend themselves to the styles of modelling to be considered below.

Perhaps the best way of representing the overall process as documented above by Weiss, is by a verbal description such as his own above, or by its representation in some graphical or schematic form. Within this overarching description, the complex systems modeller can seek embedded subsystems which lend themselves to the methods of complexity theory which we address next.

In 6.2 below, we will illustrate the use of *complex networks* in developmental systems modelling. But first let us examine the central importance of *Complexity Theory* in the more general context of the mathematics of *nonlinear systems.*

6.1 Dynamical Systems and Nonlinear Mathematics

The shape-changing processes described by Gustafson and Wolpert (*5.1.3 above*) and the idea of ‘preformed epigenesis’ as discussed by M.J.Apter, are manifestations of the concept of *emergence* which we recognise nowadays as a hallmark of *complex systems*, and indeed of life itself. *In 6.1.1 below*, we will discuss the meaning of emergence, emergent properties, and other key ideas in

complexity theory*, and in what in a sense is its converse, *chaos theory.* *In 4.2.1* above, we introduced the idea of *dynamic systems* (developed further in *6.1.2* below), and *in 6.1.3* we will arrive at the more precisely defined mathematical interpretation of complexity theory, along with some illustrative examples. *In 6.1.4* we relate the abstract ideas of complexity science to real world modelling, before taking this forward to the modelling of developmental systems using *complex networks.

6.1.1 Some Discussion of the Nomenclature of Complexity Theory

Capra and Luisi [82], p133, give the following definitions :

An emergent property is one not present in the parts and originates only when the parts are assembled together ; [cf P.Weiss's notion [89], of the *non-decomposable system*, ***in 4.1, p64 above***];

Emergence is the arising of novel properties in an *ensemble*, novel in the sense that they are not present in the constituent parts.

[Thus emergence is the essential element in the broader phenomenon of self-organisation - ***introduced in 4.4 above***.]

These notions first arose in the mid 19th Century with the *British School of Emergentism* (A.Bain (1870) [116]; J.S.Mill (1872) [117]), which maintained its influence throughout the 20th Century. (Capra and Luisi [82], p133.)

Self-organisation is the *spontaneous emergence* of *ordered patterns* in a developing system.

Emergentism is another term that can be put in opposition to *reductionism* - cf our comments on 'organicism' ***in Chapter 4, p61 above***. Thus, given that a cell is composed of a large *ensemble* of molecules, then reductionism is appropriate if restricted to the cell's *structure and composition.* 'The difference between structure and properties is fundamental. ... Emergence assumes its real value at the level of properties, and its very notion is based on the proposition that *emergent properties* cannot be reduced to the properties of the parts.'

When complexity or its companion concept of *chaos* are discussed qualitatively, clear word definitions are rarely if ever attempted. However, ***in 6.1.3 below***, the term complexity is defined more precisely in the context of *nonlinear dynamics*, and this is also the appropriate formalism for the theory of chaos. Indeed, Ian Stewart - in the Preface to his book *Does God Play Dice? The New Mathematics of Chaos* (1997) [118] - identifies the converse relationship between the two theories : 'Chaos theory tells us that simple systems can exhibit complex behaviour; complexity theory tells us that complex systems can exhibit simple "emergent" behaviour.' More recently, 'chaos' has come to be seen as one aspect of complexity theory.

Elaborating the Idea of Emergence : Capra and Luisi [82], pp154/5), explain emergence well : 'Emergent properties are the novel ideas that arise when a higher level of complexity is reached by putting together components of lower complexity. The properties are novel in the sense that they are not present in the parts : they *emerge* from the specific *relationships* and *interactions* among the parts in the *organised ensemble*. The early systems theorists expressed this fact in the celebrated phrase, "The whole is greater than the sum of its parts" '.

Some examples of emergence are also given (*ibid*, pp155/6), e.g. :

- the capacity for DNA replication emerges from the assembly of double-stranded polynucleotide chains ;

- the infectious property of a virus emerges from the assembly of viral RNA and protein mantle macromolecules ;

- life itself is an emergent property of the assembly of a cell from its subcellular components.

There are two schools of thought concerning the relationship between the properties of the basic components in a complex system, and the emergent properties of the whole :

Strong emergence, also called *radical emergence*, asserts that *in principle*, the properties at the higher hierarchical level cannot in any way be deduced from those at the lower level (e.g. J.Schrőder (1998) [119]);

Weak emergence asserts that it is only due to 'technical difficulties', e.g. insufficient manual skills, or lack of computational power, and not for reasons of principle, that the relationship between the whole and its parts cannot be established. (R.Bishop and H.Atmanspacher, eds. (2002) [120]) .

Capra and Luisi recognise a third position, based upon the systems view of life ([82], p157) : '... there is no need to assume any mysterious force to explain emergent properties

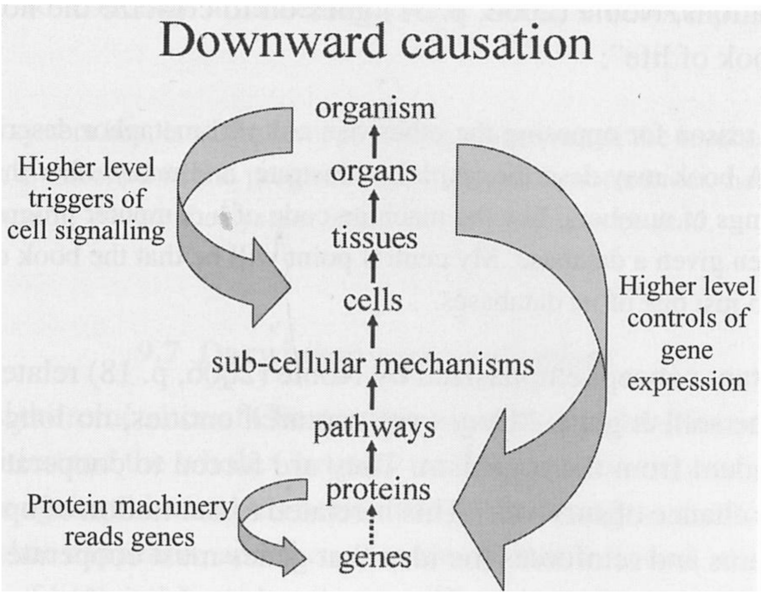

Figure 6.1.1: Downward causation, shown by the large arrows. Higher levels trigger cell signalling and gene expression. Small arrows show how genes are read and interpreted by proteins. From Fig.9.6, p205 of F.Capra and P.L.Luisi [82]

[alluding to a criticism sometimes levelled at the proponents of strong emergence], but ... the focus on relationships, patterns, and underlying processes is essential. Once this is accepted, practical difficulties will still be relevant, and the distinction between strong and weak emergence may not always make sense'. They then go on to introduce another feature of emergence :

Downward causation J.Schrőder (1998) [119], argues that while the development of emergent properties arises from an '*upward* (or *bottom-up*) *causality*', feedbacks frequently arise between higher and lower hierarchical levels, thus affecting properties at the lower level(s). (***Fig.6.1.1.***)

This feedback hierarchy can be described thus (paraphrasing from [82], p158) : ' ... the upward stream of emergence goes from the genes [as primary cause] to the proteins, tissues, organs, etc, up to the whole organism. However, it is the entire organism that determines which proteins should be built, and when. *It is the downward causation that is the primary source of biological function and behaviour*'.

Clearly, it is the control of gene expression (*gene regulation*), and *intercellular signalling* between the hierarchical levels of complexity, that is implied here by 'downward causation'.

6.1.2 Self-organisation and Emergence in Dynamic Systems

The second law of thermodynamics (***see also, 1.4.5***) establishes the principle that any isolated physical system will spontaneously follow a trajectory towards ever-increasing *disorder*. The theory defines *entropy* as a measure of the degree of disorder. Relating this to our ideas in complexity science, we must recognise that there are are two classes of self-organisation ;

Self-organisation under thermodynamic control : e.g. self-organising processes such as the folding of protein chains into their biologically functional conformations; the formation of soap bubbles; crystallisation; or the assembly of a tobacco mosaic virus from its helical RNA macromolecule and a set number of identical protein subunits; all these happen in compliance with the above second law. This is because the final assembly is more thermodynamically stable than the starting components ;

Self-organisation under kinetic control : In the language of chemistry, the *activation energy barrier* for this type of self-organisation, is much lower than the energy barrier to be surmounted if the system were to arrive at thermodynamically more stable forms. More intuitively, the kinetically controlled product is formed faster than the theoretically more stable product can be. Hence the products under kinetic control form preferentially.

In biological systems, self-organisation under kinetic control is achieved through the *catalytic action* of the class of proteins called *enzymes*. A question of great interest in developmental biology (and in the study of the origins of life) is 'What are the upper limits of complexity achievable by processes of self-organisation under thermodynamic control alone?'

Modern texts on cell biology give examples of the many subcellular (or extracellular) organelles or other nanostructures, which are capable of spontaneous self-assembly, given the appropriate conditions. (e.g. B.Alberts *et al* (2015) [53], pp128-130.) For instance, they cite the work of M.Nomura (1973) [121] on the assembly of bacterial ribosomes, and of Fraenkel-Conrat (1955) [122], on the reconstitution of active *TMV* (*tobacco mosaic virus*) from its inactive protein and nucleic acid components.

However, such (re)assembly or reconstitution, under thermodynamic control has not been convincingly demonstrated at levels of complexity above that of organelles or viruses. For instance, Capra and Luisi (2014) [82], pp152-4, cite a number of workers in this field : e.g. H.Jeong *et al* (2000) [123] on the large-scale organisation of metabolic networks with regard to *Amoeba proteus* cells ; and E.K.Pressman *et al* (1973) [124], on the reassembly of an *Acetabularia mediterranea* cell from the nucleus, cytoplasm, and cell wall.

Capra and Luisi (p154) comment on such studies that 'the reassembly is not taking place spontaneously, but, at least in one or two critical steps, is "guided" [their own "double-quotes"] by the help of micromanipulatons; [e.g.] specific enzymes and reagents are added manually during the course of the reconstitution process.' It seems, as in natural developmental systems, that the reconstitution of a cell from its molecular components (or larger subcellular assemblies thereof), must follow a precise sequence of processes in which the parts are synthesised and assembled in a predetermined order, under kinetic control.

The comparison, here, with Lewis Wolpert's question about the assembly of a paper bird by origamy (see *5.1.3*) is worth noting in the above context. *In Chapter 7*, we will return to these issues in relation to more recent work, and in particular to the fusion of our ideas about the role of *information*, of replication by *templating* or *scaffolding*, and of the involvement of *assembly factors.*

The above thermodynamic distinction has a bearing on another dichotomy distinguishing self-organising systems ;

Static self-organisation usually leads to a final *state of equilibrium* - this applies to chemical reactions or other processes under thermodynamic control in which, for instance, relative concentrations of reactants and products cease to change ; or

Dynamic self-organisation applies to systems operating far from equilibrium. These were famously studied by Ilya Prigogine as simpler physico-chemical proxies for developing biological systems. (e.g. The 'chemical clocks' of Belousov and Zhabotinsky). ***This topic is examined further in 6.1.6 below.***

To take us on to a consideration of complex systems from a more mathematical viewpoint, we note the following remark from [82], p144 : '... the most interesting self-organising systems, including many centrally important to the life of the cell, are *dynamic*; that is, they are *nonequilibrium systems* that form their characteristic *order* while *dissipating entropy*. ***This statement will be clarified in 6.1.6 below.***

6.1.3 A Mathematical Interpretation of Complexity

Complexity in the intuitive sense crops up as a phenomenon in all aspects of science, and as is apparent from everything above in this Thesis, complexity

is abundant in developmental systems in particular.

As far as *mathematical modelling* of such complex systems is concerned, the reciprocal relationship between chaos and complexity identified by Ian Stewart [118] (***see 6.1.1 above***) suggests two complementary approaches :

Set up a system based on simple rules and investigate whether these rules generate complex behaviour ;

Describe a (possibly real world) complex system and establish any emergent behaviour which is simpler to describe, e.g. by simple rules.

The first approach is the archetypal mathematical approach. The construction of the set up system, and its simple rules, will of course be informed by empirical findings if this is an exercise in applied (as opposed to pure) mathematics ;

The second approach is more akin to that of empirical science, and the 'simple rules' of emergent behaviour so ascertained might be used to construct a mathematical model to describe or explain the complex system and its behaviour.

Clearly the two approaches overlap in the use of empirical findings either to inform the construction of the model, or to verify its outcomes, or maybe both.

In the historical development of complexity theory, it was the discovery of simple mathematical mappings, with complex outcomes, that provided the initial impetus. The outcomes were perceived as chaotic, inspite of the deterministic rules of operation that generated them. Were the outcomes observed as an empirical phenomenon, they might well be perceived as random. Yet such mappings provided a deterministic explanation for these apparently complex and random outcomes. This would in time arouse the interest of empirical scientists, but initially the new theory focussed on the *simple rules → complex outcomes* aspect, under the name *chaos theory*. It also appeared under the more formal nomenclatures of *nonlinear systems theory*, *dynamic systems theory*, or *nonlinear dynamics*. In fact, after the more general term *complexity theory* became current, the above three more formal labels came to apply to it also. So the current terminology remains confusing, but the distinction between *'chaos'* and *'complexity'* alluded to above is still worth retaining.

Linearity *versus* Nonlinearity : *Linearity* is a property of a class of systems of Differential Equations (D.E.s). Such systems are easy to work with, e.g. because the sum of any two solutions is also a solution. This property does not apply to *nonlinear D.E.s.* For example the D.E for the idealised simple harmonic oscillator is linear, but that for the real pendulum (e.g. with bearing friction and air resistance) as opposed to the idealised pendulum, is nonlinear. Classically, many equations in physics are *linearised* - 'troublesome' terms which would make the equation nonlinear are discarded. Of course such linearisation is only acceptable if such terms are small and therefore 'insignificant' in magnitude. Thus classical physics often deals with low amplitude oscillations, low amplitude waves, small temperature gradients, or zero friction, and such restrictions are assumed in setting up the equations.

Mitchell Feigenbaum studied the physics of systems undergoing *phase transitions*, a recognised class of *complex processes*, the mathematics of which is nonlinear. His particular interest (M.J.Feigenbaum (1978) [125]) was the onset of turbulence in fluid flow, and its resemblance to a phase transition. The archetypal phase transitions were, of course, the changes of state in a material. The transition in turbulent flow was a change in the *flow pattern*, rather than in the physical structure of a substance. Dissatisfied with the mathematical tricks then available to deal with nonlinearity (e.g. the use of Feynman diagrams in particle physics) he turned to the abstract general problem of solving nonlinear D.E.s. For simplicity he abandoned turbulent flow, and turned to one of the simplest nonlinear D.E.s he knew of - based on the *logistic mapping.* This had already been encountered in a number of fields - e.g. R.M.May (1973) [126], and (1976) [127], had used it to explain complex behaviour in nonlinear population models.

The Logistic Mapping : This mapping illustrates another key feature of nonlinear systems, that of large effects arising from small changes in input. This comes about because the effects of small changes may be repeatedly amplified by *self-reinforcing feedback* (Stewart [118], pp145-154). Such *nonlinear feedback* is what drives the processes of self-organisation (***discussed, 4.2.2, 4.3.3, and 4.4 above***).

The feedback loops encountered here are modelled mathematically by *iteration* - a particular class of nonlinear process.

For instance, I. Stewart [118] constructs the essential features of such a process as follows:

$x_{t+1} = kx_t(1 - x_t)$ **Eq 3**

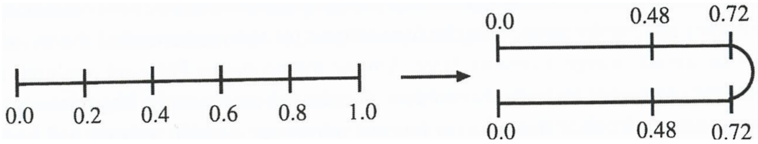

Figure 6.1.2: The baker transformation, illustrating the logistic mapping of Eq 3, for $k = 3$. Adapted from Fig.6.5, p107, *ibid* [82].

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This is the discrete dynamical system arising from iteration of the *logistic mapping*

$x \to kx(1-x)$,

where k is a constant (of most interest in the range $0 \leq k \leq 4$ - ***see below***), and $0 \leq x \leq 1$.

t represents time, advancing in discrete integer steps, 0, 1, 2, 3, ..., and x takes the value x_t at time t.

In investigating the dynamics of the system defined by **Eq 3**, the interest lies in exploring the effects of varying the parameter k. Intuitively, for chosen k, the mapping has the effect of folding the real line interval [0, 1] over itself, on top of the interval $0 \leq x \leq k/4$. (***See Figure 6.1.2 above.***) For small k this has the effect of compressing the interval, and for larger $k < 4$ the effect is to stretch the interval while folding it over itself. For $k > 4$ iteration results in the asymptotic expansion of the interval to infinity.

Varying the value of k in the range [0, 4] generates distinct *dynamic regimes* between which the behaviour of the system changes significantly. These are characterised by I.Stewart [118], pp145-154, as follows :

The Steady State Regime This is determined by setting k in the range $0 < k < 3$. For such values of k, iteration results in a sequence of values of x_t which finally reaches a constant value after a certain number of iterations. This value is termed the *point attractor* or *stable steady state* of the system for the chosen value of k. e.g. setting $k = 2$ yields a point attractor at $x = 0.5$. (***See Figure 6.1.3 ('Fixed Point') below.***)

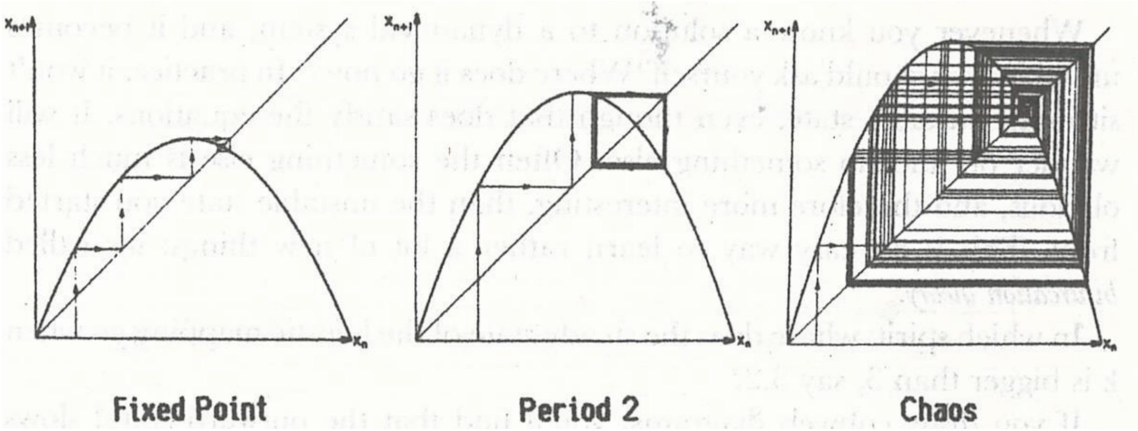

Figure 6.1.3: Use of 'cobweb diagrams' to represent the point attractor, period 2 attractor, and the chaotic regime of the logistic mapping. From Fig. 61, p147 of I. Stewart [118]

Examination of the iterative sequence of values shows how, in the cobweb diagram (***See Figure 6.1.3 ('Fixed Point')* above**), it spirals inwards towards the point attractor. For small changes in k (within the range [0, 3]), there are correspondingly small changes in the position of the fixed point.

The Periodic Regime - and the Period-doubling Cascade For $k = 3$, the convergence to a fixed point is extremely slow, and any calculation will be terminated by an apparent constant value, determined by the computational limitations of the available hardware. As Stewart points out (***ibid, p147***), 'This is a sign that we're on the verge of something dramatic'. In fact, when k just exceeds the value 3, the fixed point becomes unstable, and the cobweb diagram shows the iterative sequence spiralling outwards.

To clarify this, and to avoid the above computational problem at $k = 3$, it is best to explore what happens for $k > 3$. In the range $3.2 < k < 3.5$ (the range boundaries here are necessarily only approximate) a cobweb diagram (***see Figure 6.1.3 ('Period 2') above***) shows the outward spiral to converge to a square loop, meaning that x_t oscillates between two distinct values. So the steady state for $k < 3$ becomes unstable for increasing k, and enters a *period-2 cycle* or *period-2 attractor*.

Furthermore, as k approaches 3.5 (approximately) from below, the period-2 attractor becomes unstable, and a period-4 cycle emerges. There follows an infinite sequence of *period doublings*, to periods 8, 16, 32, 64, 128, ... , as k increases further. e.g period 8 is reached for $k \simeq 3.56$, and period 16 for $k \simeq 3.567$. **Such limiting points, at which changes in behaviour occur, are termed *critical thresholds*.**

But this rapid *period doubling cascade* is itself a convergent process, and for $k \simeq 3.58$ the period has doubled an infinite number of times ! ***Complex aperiodic be-***

***haviour* is said to have occurred, when the period has doubled *ad infinitum*.**

It is at this limiting value of k that the logistic mapping becomes "*chaotic*".

The Chaotic Regime At the value $k = 4$ alluded to above, any *trajectory* (some iterative sequence of x-values with a given starting point) will approach arbitrarily closely to every one of the (uncountably infinite) points within the real number interval [0,1]. This means that the entire interval [0,1] is the attractor when $k = 4$.

But even this does not complete the story, as there are yet more levels of complexity, even for this apparently simple, deterministic mapping. A fuller account is given by Stewart [118], pp148-154). Suffice it to say that, for our present purposes, 'buried within the chaotic regime are little "windows" of regular behaviour (Stewart, *ibid*). e.g. for k = 3.835, deep inside the chaotic regime, roughly the first fifty iterations are chaotic as expected but then, according to Stewart, the following 3-cycle appears: $0.1520744 \rightarrow 0.4945148 \rightarrow 0.9586346$. Further very small increases in k yield a new period doubling cascade : 3, 6, 12, 24, ... In fact, there are period doubling cascades for all odd numbers in increasing order, then their doubles, quadruples, ..., and finally the powers of 2 in descending order. This Theorem, determining the order in which the periods occur, was proven by A.N.Sharkovskii (1964). (*ibid*, p151; and [128] .)[3]

Stewart sums this up very nicely, [118], p151 (the *italics* are his own): '... this same bizarre ordering applies not just to iterations of the logistic mapping, but to iterations of *any* mapping on the unit interval that has only one hump. [i.e. as in a parabola- ***see Figure 6.1.3 above***]. This was the first hint that some of the patterns of chaos might be *universal*, that is, not specific to individual examples but representative of entire *classes* of systems.'

Prigogine makes a similar point, but more formally ([129] (1984), p169) in relation to what he terms the *Feigenbaum sequence*. This concerns any system whose behaviour is characterised by properties such that :

1 There is a period doubling at each of a succession of bifurcations corresponding to a set of *critical thresholds*. (***See Figures 6.1.4 and 6.1.5***);

2 The system switches from *simple periodic* behaviour to *complex aperiodic* behaviour where, at the limit, the period has doubled *ad infinitum*;

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[3] 'Sharkovskii' appears variously in the literature as 'Sharkovsky', Sarkovskii', or 'Sarkovsky' and his writings are exclusively (?) in Russian - this, apart from the maths itself, might well have been a challenge even for Thompson!)

3 As Feigenbaum discovered, such a system will necessarily generate *universal numerical features* independent of the mechanism involved.

In Feigenbaum's own words (including the *italics*), [125] (1980), 'In fact, most measurable properties of *any* such system in this aperiodic limit now can be determined in a way that essentially bypasses the details of the equations governing each specific system ...'.

It is just such a (purely mathematical) general principle which Thompson would have relished, consistent with his platonic beliefs that mathematical principles alone can constrain the ways in which systems, including those of developmental biology, must behave. (*See in particular his messages XI and XII in Chapter 1.*)

The above account illustrates the link between a dynamic system's entering an unstable state, and the emergence of a distinctly different stable state. The discontinuity between the formerly stable, and the newly emergent stable state is a key feature of *bifurcation theory.* A *bifurcation* is 'any change in the qualitative form of the attractor of a dynamical system' ([118], p151; and Figure 6.1.4 below). This theory has been developed further from the topological perspective (*see subsection 6.1.5 below*), originally under the name *catastrophe theory.* It has come to have particular significance in the study of complex systems, and biological developmental systems in particular.

Fig.6.1.5 below is a schematised *bifurcation diagram* for a dynamic system such as that generated by the logistic mapping. Corresponding computer generated diagrams visualise the entire dynamic behaviour of actual such systems for whatever range(s) of parameter values might be of interest.

As Stewart observes, 'The branches [of the bifurcation diagram for the logistic mapping] broaden into bands of chaotic attractors. [The diagram] is pocked with random dots. ... Every so often there's a thin white strip in the picture with just a few tiny dots inside it. These are the periodic windows. If you look at the window around $k = 3.835$, where the basic period is three you'll see it contains tiny ***fig-trees*** of its own. ['Fig-tree' is Stewart's description of a bifurcation diagram. [4]] ... [On magnifying one of these fig-trees further] 'you'll find that this sub fig-tree also ends in bands of chaos. Within those bands there are again white strips with just a few tiny dots. Windows within windows. In these are tinier fig-trees, and so on' [*ad infinitum*].

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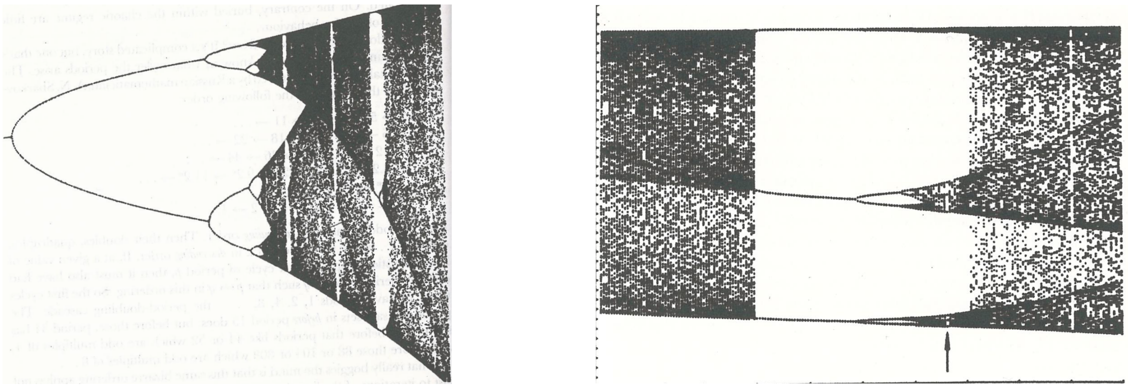
[4] Stewart admits, p152 of [118], this is his own 'Germanic pun', as 'Feigenbaum' is German for 'fig-tree'.



(a) Bifurcation diagram for the logistic mapping - constant k increases horizontally, the vertical coordinate is the state x. The fig-tree of period doublings is followed by growth of chaotic bands.

(b) Detail of (a), within the periodic window, showing how the entire structure is repeated on smaller and smaller scales - the arrows show how there are repeated windows within windows

Figure 6.1.4: (a) Bifurcation diagram for the logistic mapping. (b) Magnified detail from (a). Adapted from I.Stewart, Figs.65 and 67, pp152-3 [118]

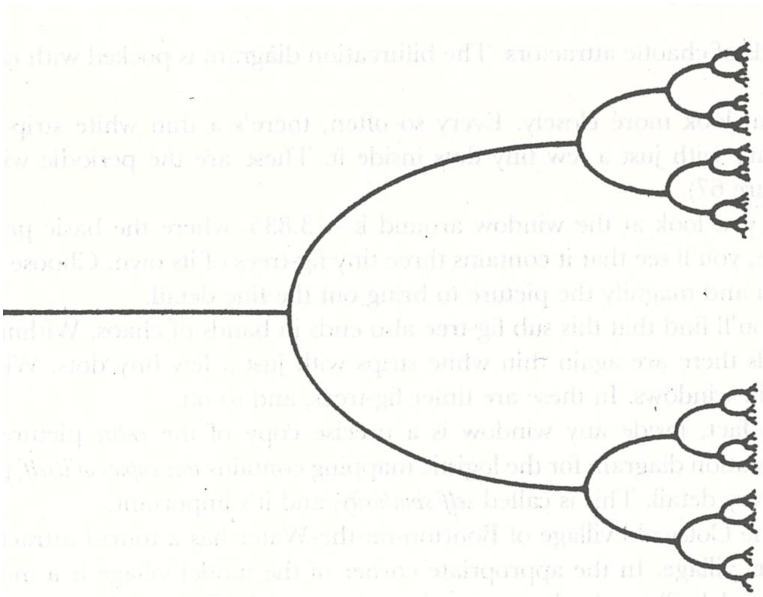


Figure 6.1.5: Schematised diagram of the logistic mapping 'fig-tree'. It shows how the curve bifurcates repeatedly, as k runs through the period-doubling regime. From Fig.66, p153 *ibid* [118]

In fact, the logistic mapping illustrates the evocative phenomenon of *self-similarity* - inside any window there is a precise copy of the entire pattern. ‘The bifurcation diagram for the logistic mapping contains tiny copies of itself, perfect in every detail’. (***ibid.***)

6.1.4 Relating Abstract Complexity Theory to the Modelling of Real World Systems

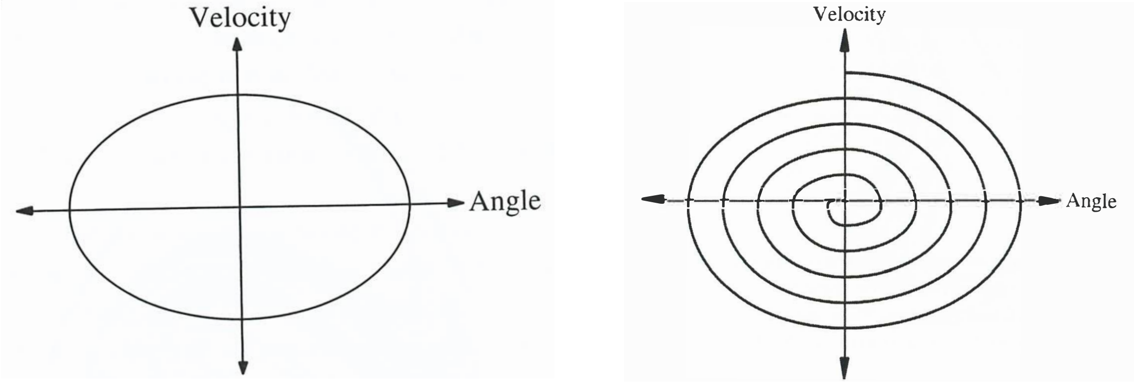
The very origins of complexity theory go back to attempts to solve the Three Body Problem in Celestial Mechanics. Henri Poincaré (1890) [130] published the memoir *On the problem of Three Bodies and the Equations of Dynamics.* This established some general properties of dynamical equations, tackling in particular the question of the existence of periodic solutions to D.E.s, and attempting to apply these results to the problem of arbitrarily many bodies moving under gravitation. His analysis came up with infinite series expansions, whose terms were periodic functions of time. But he could not prove that these expansions were in general convergent. However, as I.Stewart cites [118], p58, Poincaré believed that ‘From these results, [it follows] there exist series whose coefficients are periodic and which formally satisfy the equations’. Instead of attempting to prove (as we now know) a falsity, Poincaré went on to say , ‘... I shall, by looking at the question from another point of view, rigorously demonstrate the existence of periodic solutions, which implies the convergence of the series’.

In the process he was to demonstrate the futility of this claim, but his ‘other point of view’ turned out to be the invention of a new branch of mathematics, *topology*, and a century later this would lead to the mathematics and science of *complexity.*

In elementary terms, topology is a kind of geometry, commonly characterised as ‘rubber sheet geometry’. More precisely it is a mathematics of *continuity*, in which lengths, angles, shapes, and areas are infinitely mutable (see [118], pp54-55). It concerns only those properties of shapes that are unchanged (*invariant*) under *reversible continuous transformations.* (That is, the operation of reversing the transformation must also be continuous.)

In terms more in line with our considerations in developmental biology, topology is a geometry of patterns and structural relationships. All forms which can be transformed into one another by continuous ‘bending, stretching and twisting are termed “*topologically equivalent*”. ... Topology is a mathematics of relationships, of unchangeable, or “invariant” patterns’. ([82], p108.)

Poincaré applied his methods to a simplified version of the 3-body problem (*Hill’s reduced model*), effectively comprising two fixed planet-sized objects orbited by a dust particle, with no external gravitational influences. His approach was essentially as follows:



(a) Trajectory in phase space of the idealised frictionless pendulum

(b) Trajectory in phase space of a pendulum with friction

Figure 6.1.6: The two-dimensional phase space of a pendulum with, and without friction. Adapted from Figs.6.7 and 6.8, p111 of F.Capra and P.L.Luisi [82]

- Assume at some time t that the system is in a particular *state*, and that at a certain later time $t+\delta t$ it is in the identical state - i.e. all positions and velocities are exactly as at time t, simultaneously.

- Then the uniqueness of solutions to D.E.s must mean that the dynamics has transformed the state back to itself, and the motion must be *periodic*.

- The state of the system is described by coordinates in a high dimensional *phase space*. In the case of the above system, as well as the usual coordinates of time and space, this will include a velocity coordinate. In generalised dynamic systems the phase space may be of arbitrarily high dimensionality.

- The path the state of the system follows through phase space is termed its *phase space trajectory*. If a point in phase space traces out a closed loop trajectory, then its motion is periodic.

The above principles are illustrated in ***Figure 6.1.6***, which shows the 2-dimensional phase space of a pendulum, and the trajectories for an idealised pendulum with no friction (***Figure 6.1.6a***), and another for a pendulum with friction (***Figure 6.1.6b***).

Poincaré developed a method, now known as the *Poincaré section*. Instead of examining all possible *initial states*, this involves only a small subset of them. This subset represents a surface of initial states embedded within the overall multidimensional phase space. The evolution of each such state is traced until (if ever) it intersects the surface again. Any such state which does return to precisely the same point in the section determines a periodic solution.

When he applied this to Hill's reduced model, he was able to determine the general shape of its trajectories, involving paired intersecting curves.. However, this was to be the first encounter experienced by any investigator, with trajectories in the chaotic regime of a nonlinear dynamic system (***see 6.1.3, p106 et seq***). Paraphrasing Poincaré's own words, but avoiding some deep technicalities : 'When one tries to depict the figure ... and the curves' infinity of intersections, ... [they] form a kind of net, web, or infinitely tight mesh; neither of the two curves can ever cross itself, but must fold back on itself in a very complicated way in order to cross the links of the web infinitely many times. One is struck with the *complexity* of this figure that I am not even attempting to draw. Nothing can give us a better idea of the *complexity* of the three-body problem.' (Adapted from the citation in [118], pp62-3.)

As Stewart interprets it (***ibid***), 'Poincaré's discovery ... means that very complicated dynamics can occur in something as simplified as Hill's model. A system that starts at an intersection point of the web traces out a curve which, when it returns to the Poincaré section, hits the web at another intersection point, then another, then another. But the web is stretched and folded in such a complicated way that effectively the system passes through the Poincaré section at a random sequence of points.'

With the mathematical techniques, and computational capabilities available to him, Poincaré could pursue the properties of these chaotic attractors little further, but this would change with the advent of high speed computers.

Quantitative *versus* Qualitative Analysis in Nonlinear Dynamics Poincaré's discovery would not be pursued further until computers became widely available from the 1960s. So progress in the science of chaos and complexity awaited this technological advance. In addition, most nonlinear equations describing natural systems cannot easily, if at all, be solved analytically. So sophisticated numerical techniques had to be developed, whose application was facilitated by the availability of fast computational capability. The established routine is to apply Poincaré's topological methods as follows :

- model a complex system with a system of nonlinear differential equations ;

- solve this system numerically ;

- use computer graphics to plot the solutions as trajectories in phase space.

There is an important difference between a solution obtained analytically, and one obtained numerically :

An analytical solution provides a formula which enables precise calculation of variable values for each state of the system, whereas

A numerical solution comprises a data set of values for all the variables, satisfying the nonlinear equations.

The analytical approach in the above context is therefore often termed ***quantitative analysis***, whereas the numerical approach, displaying the solution visually in the form of a graphic, is termed ***qualitative analysis***.

This qualitative approach has provided the means to uncover the *order* underlying apparently chaotic phenomena, as exemplified in our discussion above (***in 6.1.3, pp106 et seq***). In the study of complex systems in general, it was surprising that in the topological classification of their dynamic properties, only a small number of distinct types emerged. These correspond to the three dynamic regimes we discussed above, each associated with a particular type of *attractor* :

point attractors corresponding to systems reaching a stable equilibrium;

periodic attractors corresponding to systems undergoing periodic oscillations; and

chaotic attractors corresponding to chaotic systems.

A popular term for a chaotic attractor is a *strange attractor*. ***Figure 6.1.7 below*** exemplifies a strange attractor in two-dimensional phase space.

This simple classification of types of complex system dynamics supports I. Stewart's observation that 'complexity theory tells us that complex systems can exhibit simple emergent behaviour' (***6.1.1, p102 et seq***). Another important such simplification is that 'strange attractors tend to be of very low dimensionality, even in high-dimensional phase space' ([82], p113). For instance if a system comprises, say 100 variables, but its motion is confined to a strange attractor of 3 dimensions, then this represents a *high degree of order*.

A further aspect of order is that all trajectories, starting from a defined region of phase space, must necessarily find their way (if not already within it) to the same attractor. This region is termed the *basin of attraction* of the corresponding attractor. So the phase space of a nonlinear system can be *partitioned* into a number of basins of attraction, each of which contains its corresponding *embedded attractor*.

Thus, the overarching outcome of the qualitative analysis of a dynamic system comprises the identification of its set of attractors and their corresponding basins, each classified in

Figure 6.1.7: The Ueda attractor - a ‘strange attractor’ in two-dimensional phase space. The logistic mapping again underlies the system dynamics, which models that of the chaotic pendulum. From Fig.6.9, p113 of F.Capra and P.L.Luisi [82]

terms of their topological properties **- *see above classification of attractors***.

The resulting dynamical description of the entire system is termed its *phase portrait.*

As Capra and Luisi claim (***[82] ibid***), ' ... chaotic behaviour, in the new scientific sense ..., is very different from random, erratic motion. With the help of strange attractors a distinction can be made between mere randomness, or '*noise*', and chaos. Chaotic behaviour is deterministic and *patterned*, and strange attractors allow us to transform the seemingly random data into *distinct visible shapes*.'

Substituting '*forms*' for '*shapes*' in the above quotation, and noting the reappearance of '*pattern*' in the discourse, yields yet another nice link back through the decades to the thinking of D.W.Thompson. Though he does not make any use of the term 'pattern' in OGF(1), he does add a 'A Note on Pattern', pp1090-92 of OGF(2), where he states 'We have had so much to do with the study of form, that pattern has been wellnigh left out of the account, although it is *part of the same story.* Like any other aspect of form, pattern is correlated with growth, and even determined by it'.

6.1.5 Spontaneous Emergence of Order in Developmental Systems

The mathematical methods originated by Poincaré were developed further in the early 1960s by the topologist Stephen Smale (e.g. S.Smale (1966) [131] and (1967) [132] , following significant advances in topology as a pure mathematical discipline in the interim. As well as establishing the phase portraits of systems described by sets of nonlinear D.E.s, Smale went on to study how the system dynamics changes with small changes in the parameters of the equations. He discovered the property of *structural stability*, whereby the shapes of the attractors and their basins (the phase portrait) undergo smooth changes as the equation parameters change smoothly and slowly. The basic topological characteristics of the phase portrait, however, remain unchanged.

But there are nonlinear systems, for which small changes in some parameters can affect the fundamental topological characteristics of the phase portrait - e.g. new attractors may arise, some attractors may disappear, or they may transfom into one another across the phase portrait. Such systems exhibit *structural instability.*

Structural stability and instability provide a generalised setting for the mathematical interpretation of complexity ***as discussed in 6.1.3 and 6.1.4 above***, and exemplified by the logistic mapping in particular,. The points at which *phase changes* (i.e. changes in the system's phase portrait) suddenly occur are termed *critical points*, or *bifurcation points*. They are points in the development of the system (often the term 'evolution' is used in this context rather than 'development') at which a fork appears in the developmental process, and the system makes a choice as to which branch of the fork it follows. (***See Figure 6.1.5, p113 above***, showing a schematic bifurcation diagram.)

So topologically speaking, sudden changes in the system's phase portrait occur at bifurcation points. In physical terms, 'bifurcation points correspond to points of instability at which the system changes abruptly and *new forms of order* suddenly appear'. ([82], p116.)

Thinking specifically in terms of developmental systems, the above ideas suggest the following characterisation. In a developmental system, for a given set of values of the system parameters, the phase portrait describes the current state of the system as a whole. If the system is structurally stable, then small, time-variant changes in parameters will result in correspondingly small changes in the phase portrait as the system develops. In a structurally unstable system, the phase portrait will change abruptly if the changes in parameters bring the system to a point of instability.

The relevance of the above mathematical theory to modelling the processes encountered in developmental biology is clearly apparent. I.Prigogine was a leading proponent of topological methods in the mathematical modelling of structurally unstable systems, relating all this to the concept of 'emergence' ***discussed in 6.1.1 above***. e.g. Capra and Luisi put it as follows :

'... spontaneous emergence of order at critical points of instability - often referred to simply as "emergence" - has been recognised as one of the hallmarks of life ... . The elucidation of its underlying dynamics, pioneered by the physical chemist Ilya Prigogine, is perhaps the most important contribution of complexity theory to the systems view of life'. ([82], p76.)

6.1.6 Ilya Prigogine's Theory of Dissipative Structures

Examples of static self-organisation (***see 6.1.2 above***), spontaneously producing high levels of order, were well known and understood in chemical and simple biological systems in the early 1960s. It was then that Ilya Prigogine achieved a significant advance in the theory of the poorly understood dynamical systems, open to flows of matter and energy. Although such systems change over time, and operate far from equilibrium, they are yet capable of generating stable, self-organising patterns or structures.

Prigogine, and his team at the Free University of Brussels pioneered work in the analysis and mathematical description of the processes of dynamic self-organisation (***6.1.2 above***). Crucial to this was their realisation that systems far from equilibrium must be described by systems of nonlinear equations. So they were able to apply the newly available mathematics of complexity to, in the first instance, nonequilibrium physical and chemical systems, which stood as simpler proxies for living systems.

Over the next decade, the work culminated in the *Theory of Dissipative Structures.* (e.g. Prigogine and Stengers (1984) [129].) The types of systems studied included :

Bénard cells - these demonstrate *Bénard instability* (e.g. in thin layers of silicone oil), resulting in an emergent pattern of regular hexagonal convection cells, arising from special forms of heat conduction.

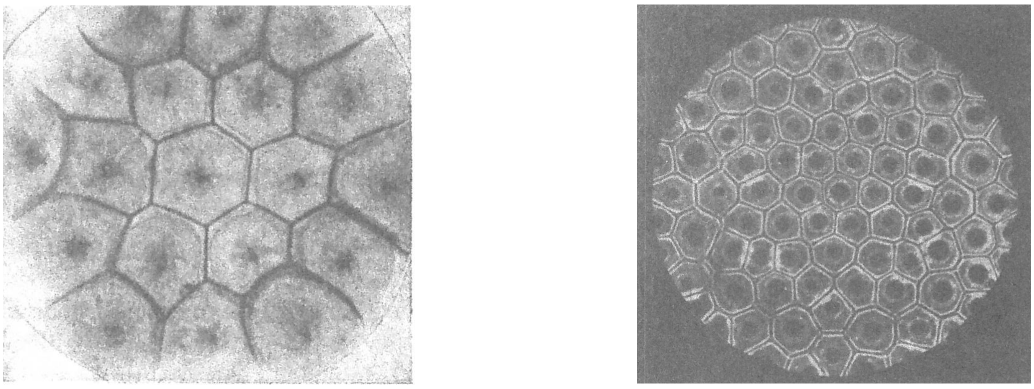
The pattern emerges (at a critical point of instability) as the system moves away from the equilibrium condition of uniform temperature throughout the liquid;

Chemical Clocks - complex systems of chemical reactions, some autocatalytic, operating far from chemical equilibrium, producing periodic oscillations in the concentrations of reactants and products. The set of nonlinear D.E.s describing such reactions came to be known eponymously as '*Brusselators*'.

For other examples of emergence in dynamical systems, e.g. involving signalling interactions between bacterial cells, see [82], pp161-163. Emergent phenomena in such cases include formation of biofilms, enhanced capability of bacteria to colonise eukaryotic organisms, or the production by pathogens of virulence factors.

Fig.6.1.8 shows some simple examples of spontaneously ordered structures.

In effect, Prigogine *et al* had used complexity theory to develop a new theory of *nonlinear thermodynamics.* The following quote from Prigogine and Stengers (1984) [129], is used in [82], p159, to explain further : 'Classical thermodynamics leads to the concept of '*equilibrium structures*' such as crystals. Bénard cells are structures too, but of a quite different nature. That is why we have introduced the notion of '*dissipative structures*', to emphasise the close association, at first paradoxical, in such situations between *structure and order* on the one side, and *dissipation* ... on the other.'



(a) Pattern emerging when coloured drops of sodium chloride diffuse into a less dense solution of the same salt

(b) Pattern emerging from the diffusion in gelatine of drops of potassium ferrocyanide solution

Figure 6.1.8: 'Artificial tissues' formed in simple diffusion experiments (after Leduc). From OGF(1). Figs.122 and 123, p320

In the theory of classical thermodynamics, 'dissipation' alludes to the degrading of energy in processes such as friction and transfer of heat. In engineering terms this is associated with wasted (lost or unusable) energy, and physically to a decrease in order, and increased entropy. By contrast, the concept of a 'dissipative structure' introduces a paradigm shift, highlighting that in *open systems* (open to flows of matter and energy) 'dissipation' becomes a source of order and therefore (locally within the system), a decrease of entropy.

cf the earlier ideas of von Bertalanffy and the cyberneticists. (Chapter 4, pp61-62 above.)

The relevance of Prigogine's idea to developmental processes is that, whilst sustaining a stable condition far from equilibrium, dissipative structures may also develop (or 'evolve') from one state to another, and by continuous or discrete change. As Capra and Luisi have put it ([82], p159) : ' When the flow of energy and matter through [open systems] increases, they may go through new instabilities and transform themselves into new emergent structures of increased complexity. In the language of nonlinear dynamics, the system encounters bifurcation points, each characterised by a specific attractor, where new structures and new forms of order emerge.'

Let us conclude our discussion of Complexity Theory, by considering a distinct form of mathematical modelling - the *complex network.* This applies another relatively new branch of mathematics, *network theory.* It is appropriate for modelling systems so complex, and with so many mutually interdependent variables, that the nonlinear D.E. approach alone would be intractable. The network approach copes better when high levels of dimensionality, and huge

numbers of parameters are involved.

In [82], p181, we are reminded how the '*ensemble*' is an essential ingredient in the modelling of complex developmental processes. The *ensemble* is also essential in particular, in the network approach to modelling complexity. The key feature of a network ensemble is its *nonlocalisability* within the network :

'Life, ..., is one of those phenomena that cannot be explained in reductionist terms. One could never grasp the essence of a rose by saying that it is composed of atoms and molecules. An "emergentist" approach ... would be to consider its ontogeny [development], pausing at each level of growing complexity, in order to study the corresponding emergent properties - from the formation of the various flower cells to the interactions between all these cells, and up to the characteristics of the complex organs, such as petal and stem, including odour and colour. We would then consider the rose as the final "flowering" of all these emergent properties.'

'The notion that one arrives at in the end is that the rose is an ensemble of various emergent properties - the colours, the perfume, the symmetry - without any central localisation where the essence of the rose would be condensed. .... we ... [encounter] ... the concept of an ensemble when asking the question "What is life" ?'

The emergent properties of a complex network are also non-localised *global properties*, and such a network does indeed generate these properties as an ensemble. It requires the network as a whole to do this, as it is the interactions between all of its parts which generate the ensemble of properties which characterises the network's structure and functioning.

Thus, complex networks, as we shall see *in 6.2 below*, are an effective way of modelling developmental systems. (*cf 4.2.1, pp65-6 above.*)

6.2 Dynamics on Complex Networks

6.2.1 Some Historical Links Between Network Modelling and the Ideas of D'Arcy Thompson

In his (still very influential) book *The Origins of Order : Self-organisation and Selection in Evolution* (1993) [81], Stuart A. Kauffman makes the claim (p443) that, rather than arising just through the evolutionary processes of natural selection, 'order in organisms may largely reflect *spontaneous order in complex systems*', and that it is upon such spontaneous order that selective processes can then act. This, and related claims in the fields of both Evolutionary Theory and Developmental Biology, are to be found throughout the book.

It is worth comparing this viewpoint with that of D'Arcy W. Thompson, in which he puts forward his *Theory of Transformations* (***see Thompson's messages XI amd XII, pp13-15 above***). Thompson's view was at variance with the Darwinian viewpoint of his time, in positing that species evolve from one into another by global transformations spanning the body as a whole, rather than through a succession of small scale changes affecting particular components of the organism.

For instance, he observes in OGF(1) ([2], p727) that '... the morphologist ... when comparing one organism with another, describes the differences between them point by point, and "character" by "character". ... and he falls readily into the habit of thinking and talking of evolution as though it had proceeded on the lines of his own descriptions, point by point and character by character'.

He had no argument with the Mendelian viewpoint, however, though he only mentions this in OGF(2) where he elaborates on the above statement ([3] p1036) as follows :, '... the "characters" of Mendelian genetics, ... , tall and short, rough and smooth, plain or coloured are opposite tendencies or contrasting qualities, in plain logical contradistinction'. [The "double quotes" in this, and the above paragraph are all Thompson's own.]

However, Thompson saw the need also to consider holistic change across the whole body. He goes on to say (OGF(2), pp1036/7), ' ... rather is the living body one integral and indivisible whole, in which we cannot find ... any strict dividing line even between the head and the body, the muscle and the tendon, the sinew and the bone.' Moreover, in relation to his Theory of Transformations (***see message XI, pp13-15 above***), he goes on to say 'The coordinate diagram throws into relief the integral solidarity of the organism, and enables us to see how simple a certain kind of *correlation* is [Thompson's emphasis] which had been apt to be a subtle and complex thing'. (***For more on this topic, see***

subsections 5.1.3, and 6.1.1 above, and also the introductory paragraphs to this Chapter, pp99-101.)

By ‘correlation’ above, Thompson alluded to a philosophical problem of the time, concerning how the separate and discrete sets of characters implied by the ‘gene-free’ Darwinism of the time, could vary together in such a way as to evolve (or develop) the characters of an integrated whole organism. (e.g, H.F.Osborn’s assertion (1915) [133], that a ‘*principle of hereditary correlation* combined with a ‘*principle of hereditary separability* [determines that] the body is a colony, a mosaic, of single individual and *separable* characters’. (See OGF(1) [2], p714; and the footnote, p727.)[5]

Of course, Kauffman’s ‘spontaneouss order in complex systems’ can allude to the types of holistic change put forward by Thompson, though Thompson tended to think of the underlying mechanisms of such change in terms of physical and chemical processes alone. Although he refers to the Mendelian idea of a gene (*see above quotation*), he could have little idea in 1917 (or even 1942) of what a gene was, or how it operated. Apart from his Theory of Transformations, Thompson concerns himself (in most of his book) with the development of very simple organisms or structures, whose development can be explained in terms of well understood physicochemical processes alone.

We have already remarked - *e.g. in Sections 1.1 and 1.2*, on Thompson’s concerns very early on ([7] and [8]) that anatomical homologies are not adequately explained by common descent alone, and the transmission of heritable characteristics (e.g. [2], p251).

6.2.2 Modelling the Dynamical Behaviours of Gene Regulatory Networks (GRNs)

One key focus in Kauffman’s work was the modelling of such processes as cellular differentiation, pattern formation, and morphogenesis in Developmental Biology. In this regard, he stressed the central importance and applicability of *Boolean Networks (BNs)* in the mathematical modelling of the processes of self-organisation and evolution in GRNs. This starts with the *Boolean Idealisation*, which posits that the activity state of a regulated gene is either *active* or *inactive*, and that its products are either present or absent (M.Sugita (1963) [134]. The effects of molecular signals controlling any particular gene are described by a class of *logical switching function* - termed *Boolean Functions* by Kauffman. (**cf the *neural networks* described in 4.2.3, pp68-9 above.**)

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[5] ‘Osborn’ appears as ‘Osborne’ in the index of OGF(2), but nowhere else in either edition of OGF.

Much research in the years since Kauffman's paper on metabolic stability and epigenesis in randomly constructed genetic networks (S.A.Kauffman (1969) [135]) has sought to elaborate on this approach, and on the ideas outlined above. Kauffman's book, [81], was one of the first attempts at reviewing this work, thereby approaching the problem of development from a more quantitative, generalised, and therefore mathematical standpoint.

Since its publication, there has been great interest in, and elaboration of the mathematics of networks, prompted by the concurrently rapid developments in Computer Science. There are now many more mathematical and computational tools available to enable development of theories and models along the lines initiated by Kauffman. M.E.J. Newman's text, *Networks, An Introduction* (2010) [136] is a comprehensive account of Network Theory, and its multidisciplinary applicability as it stands today.

Much current research, ***to be reviewed briefly in sections 6.3 and 6.4 below***, takes Network Theory as its vehicle for investigating the origins of spontaneous order in complex biological systems, in particular GRNs. In so doing, it contributes to a busy field of research on spontaneous order, most of which approaches the problem from the evolutionary perspective. Many of the ideas in the latter field can be applied as effectively in the area of biological development, and it is to be expected that aspects of the two approaches should be seen as complementary. In fact a more realistic viewpoint may well be that evolution operates upon developmental systems, and not just upon the adult organism.

We start, *in 6.2.3 and 6.2.4 below*, with a quick look at the models as originally proposed by Kauffman. Then, *in 6.2.5*, we take note of their reformulation in more recent work, inspired by the modern developments in mathematical Network Theory. As an example, we discuss a simple toy model specified by the use of *undirected, signed networks*, whose evolution in time is determined by a particular variation of the *majority rules (MR) updating procedure* (*explained below).*

6.2.3 State-space Dynamics of Boolean Networks

Kauffman defined the activity state of any regulated gene as a function of the presence or absence of the regulating variables - usually gene products such as proteins, RNAs, or metabolites. Within an entire genetic network, each *regulated gene* will respond to a set of other genes (*regulating*, or *regulator*, *genes*) whose products regulate its activity,

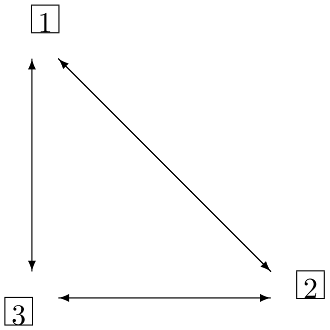

Figure 6.2.1: A 3-node network in which each node is linked to each of the others, by Boolean functions.

either *positively* or *negatively.*[6] Moreover, all the genes in a network (GRN) may respond simultaneously to the outputs of the genes which regulate them. (This simultaneity of response is the assumption made in many, but not all, of the more recently investigated network models.) So this methodology deals with *parallel-processing networks*, and not so much with models conceived around the often used, but misleading, term 'genetic program'. (***See 3.5, pp58-60 above.***)

This leads on to the idea of *state-space dynamics*, which was interpreted by Kauffman in terms of Boolean networks.

To help formalise this idea more, consider a hypothetical autonomous network - one which has no inputs from outside the system. We construct the system for each element (a gene in the case of GRNs) among the N elements in the system, a subset of K elements of which will serve as its regulatory inputs, $K \leq N$.

For illustrative purposes, let $N = 3$, and assume each of the three elements to be regulated by the other two in the network, as indicated by the arrows ***in Figure 6.2.1*** :

Then, to set the rules for state changes, we assign to each regulated binary element, which can be in state 1 or 0, one of the possible **Boolean functions** for k=2 inputs, ***as shown in Table 6.2.2 below***. Suppose element 1 ***in Figure 6.2.1*** is regulated by the Boolean AND function, and that elements 2 and 3 are each regulated by the OR function, ***as shown in the truth tables in Table 6.2.2***.

The state of the regulated element after it is acted upon by the respective function appears in column 3 of its truth table. The input states of the two regulating elements appear in columns 1 and 2. Thus, in the table for Element 1, acted upon by the 'AND' function, the *next state* of Element 1 is zero if both input states are zero, or if just one or the other

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[6] Often, in modern (especially biological) texts, 'positive' and 'negative regulation' are referred to respectively as '*up-regulation*' and '*down-regulation*'.

Element 1			**Element 2**			**Element 3**		
2	3	1	1	3	2	1	2	3
0	0	0	0	0	0	0	0	0
0	1	0	0	1	1	0	1	1
1	0	0	1	0	1	1	0	1
1	1	1	1	1	1	1	1	1
‘AND’			**‘OR’**			**‘OR’**		

Table 6.2.2: The Truth Tables for Elements 1, 2 and 3 in Figure 6.2.1

T			**T + 1**		
1	2	3	1	2	3
0	0	0	0	0	0
0	0	1	0	1	0
0	1	0	0	0	1
0	1	1	1	1	1
1	0	0	0	1	1
1	0	1	0	1	1
1	1	0	0	1	1
1	1	1	1	1	1

Table 6.2.3: Showing the Set of Possible State Transitions for the Entire System in Figure 6.2.1 and Table 6.2.2

inputs is zero, but its next state is 1 if both input states are 1.

We make the further simplifying assumption that this network is *synchronous*, whereby each element enters its next state as determined by its respective Boolean function, simultaneously with all other elements. Then ***Table 6.2.3 above*** shows how the next activity state of each element 1, 2 and 3, changes from time T to time $T + 1$, due to the action of the Boolean functions.

In this way, the system as a whole passes between time steps, each to its own unique *successor state*, and over a sequence of such time steps, will follow a sequence of successor states called a *trajectory*.

From this table we can construct a *state transition graph* (or *behaviour field*) of the Boolean

Basin 1	**Basin 2**	**Basin 3**
		100
		⇓
000 ⇔ 000	**001 ⇔ 010**	**110 ⇒ 011 ⇒ 111 ⇔ 111**
		⇑
		101

Table 6.2.4: The Three Basins of Attraction in the System of Fig.6.2.1, and Tables 6.2.2 and 6.2.3

network by showing the state transitions to successor states by *directed links* (arrows) ***as shown in Table 6.2.4***.

These graphs demonstrate that as there are a finite number of states of the system, once the system re-enters a state already encountered in it trajectory, then it must recycle repeatedly through this recurrent sequence of states (thus forming a *state cycle*). In principle there may be state cycles of length up to 2^N. In this example there are three state cycles„ each of length 1. The state cycles are the *dynamical attractors of the Boolean network.* The set of states which flow into a particular state cycle constitutes its *basin of attraction.*

Thus we see that any such network must have at least one state cycle (*attractor*). In the above example there are three. Also, each state can transition into only one attractor (if not already inside it), and the set of attractors constitutes the *dynamical attractor* of the system as a whole. The set of attractors, plus their respective basins, must partition the *state space* of the system, which must comprise 2^N states in all.

6.2.4 Effects of Perturbations on a Specified System and the Biological Interpretation of State Space Dynamics

Many variations on the above type of model have been tried and tested in the time since Kauffman studied Boolean networks and functions. It has been instructive in the conduct of such research to study the effects on a specified system of two types of perturbation :

1 A *minimal perturbation*, such as the transient flipping of the activity of one element to the opposite binary state. Such studies are of interest in the investigation of the *stability* (or *resilience*) of attractors to such perturbations (also termed *robustness* in many studies). ***For a recent, more sophisticated example, see 6.4.4 below.***

Basin 1	**Basin 2**	**Basin 3**
100 ⇓ **110 ⇒ 001 ⇒ 000 ⇔ 000** ⇑ **101**	**011 ⇔101**	**111 ⇔ 111**

Table 6.2.5: Effects of a Structural Perturbation on the Attractors and their Basins in Table 6.2.4

2 A *structural perturbation* is a permanent alteration (maybe a *mutation* in the biological context) in the Boolean functions (or other types of state transition operator in related models) defining the network. ***Table 6.2.5*** shows the effect on the state transition graph of the Boolean network discussed above, mutating the *rule* governing element 2, from the OR function as above, to the AND function :

The diagrams and descriptions of the Boolean function discussed above are all adapted from Stuart Kauffman [81].

Kauffman interpreted a *cell type* as a recurrent pattern of gene activity, and hence as an attractor in the GRN governing the cell dynamics. The analogy with dynamical attractors seems a good one, though the idea still proves controversial.

Suffice it to say for now that the state cycles comprising recurrent patterns of states in the variables of the system typically occupy a small subvolume of the entire state space. This can be a helpful feature in this type of model, as a cell type arises from the integrated dynamical behaviour of a coupled system, potentially comprising thousands of genes and their products, all of which have the potential to regulate - that is to activate or deactivate, accelerate or decelerate the activity of - one another.

6.2.5 Elaboration and Diversification of Models based on Complex Networks, beyond Boolean Networks

Two broad sets of objectives have motivated complex network modelling of GRNs since Kauffman's pioneering work.

A. The Characterisation of the Local Features of GRNs. For instance:

1 . Investigating how many genes or gene products directly regulate a given gene, and how that gene responds to each regulatory input. This can be studied for any specific gene of interest, or averaged over a sample of GRNs - the general expectation is that any gene is regulated by a small number of factors, and so the respective GRN is *sparsely connected* ;

2 Investigating whether particular classes of Boolean functions (or related models of regulatory inputs developed more recently) regulate all, or almost all, known genes. For instance, Kauffman himself characterised one such class of functions, which he termed *canalising functions* ;[7]

3 On the assumption that GRNs are constrained to have such local properties, to investigate the implications for the structure, and integrated behaviour of such systems.

B. The Use of Ensemble Theories

The Boolean switching (or related) models have frequently been applied in this context, entailing the investigation of an ensemble of GRNs, the members of which show the properties emerging from the above local features of GRNs.

Of course, the number of such GRNs in an ensemble is necessarily huge, and so studies focus on their statistical properties. In the process, assessments may be made as to whether or not the typical ensemble properties can be related to local properties of the networks.

Kauffman, in [81], takes this a step further in claiming that ‘almost all’ members of a GRN ensemble show many of the ordered properties seen in the real world processes of ontogeny.

The example in the next subsection illustrates how such problems can be approached using the more recently developed concepts and methods of Network Theory.

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[7] Kauffman’s terminology here was inspired by Waddington’s use of the term *canalisation* in his conception of the *epigenetic landscape* - ***see 3.4, pp55-57 above.***

6.2.6 A 'Toy Model' to Exemplify how the Modelling of GRNs has Progressed Using Network Theoretic Methods

This model is less cumbersome than the use of Boolean functions. It takes as input a set of column vectors, each representing a possible state of the dynamic system, modelled in this case by a *signed network*. The elements of the input vector can take only the values +1 or -1, analogous to a Boolean network, but with -1 substituting for the Boolean zero.

The *state transitions* are generated by the action of an *adjacency matrix* (also termed the *transition* or *updating matrix*) which represents the network in question. The algorithm (***see below***) then finds the *set of attractors* generated, given a particular input vector (representing an *initial state* of the system), and a selected adjacency (transition, or updating) matrix, representing the network structure (*topology*). Because we are dealing with signed networks, the entries in the adjacency matrix can take the values +1 or -1 (for positive or negative links respectively), or zero (the latter signifying the absence of a link, as in unsigned networks).

Thus, the algorithm inputs one *state vector*, and outputs another, by the operation of the adjacency matrix A, which can also be provided as input. The elements of each input, taking the values +1 or -1, are subject to an *updating procedure* operating by a specific set of *updating rules*. This particular example uses a variation of the *Majority Rules (MR)* updating procedure, discussed further below ***in 6.4.2***.

It is worth referring back to the cyberneticians' definition (*in 4.2.1 above*) of an *effective dynamic system*, to see how this concept carries over very nicely to currently used classes of network models, as discussed here.

Next, we illustrate the workings of the above algorithm using a simple example of a 3-node signed network, and a particular 3 X 3 adjacency matrix, A, as operator. We make the further simplifying assumption that the signed networks are *undirected* - that is, in this particular model, there is no sense of direction in the links joining adjacent nodes. This would correspond to a 'real' network in which there was a mutual up-regulation, or a mutual down-regulation between nodes joined by a positive or negative link, respectively. ***See footnote 6, under 6.2.3 above.***

In Figure 6.2.6 below, nodes 1 and 2 are connected by a positively signed link, and nodes 1 and 3 by a negatively signed link. There is no link between nodes 2 and 3.

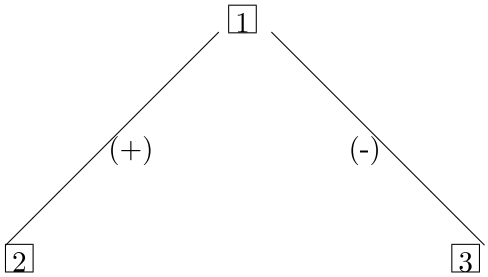

Figure 6.2.6: A 3-node, undirected, signed network.

The adjacency matrix, A, for representing this network is :

$$A = \begin{pmatrix} 0 & 1 & -1 \\ 1 & 0 & 0 \\ -1 & 0 & 0 \end{pmatrix}$$

A operates on input vector x by matrix composition, as follows, yielding updated state vector x', where x and x' are represented by column vectors :

$$x' = Ax \quad \textbf{Eq 4}$$

Thus, suppose $x = \begin{pmatrix} -1 \\ -1 \\ 1 \end{pmatrix}$ then $x' = \begin{pmatrix} -2 \\ -1 \\ 1 \end{pmatrix}$ in **Eq 4**.

Generalising the notation, and writing the ith element of x to be x_i, and the ith element of x' to be x'_i, then we can represent such a transition as:

$$\begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} \rightarrow \begin{pmatrix} x'_1 \\ x'_2 \\ x'_3 \end{pmatrix}$$

Then the particular variation of the *MR procedure* used in this model operates by a specific set of *updating rules*, defined as follows, using the above notation:

If in vector Ax, element $x'_i > 0$, then the new value of x'_i is set at $+1$;

If in vector Ax, element $x'_i < 0$, then the new value of x'_i is set at -1;

If in vector Ax, element $x'_i = 0$, then the new value of x'_i stays as x_i.

So the rule applied here sums the signs of the links connecting each node within any pair of adjacent nodes, and the *next state* of each node is +1 if the sum is positive, -1 if the sum is negative, and remains unchanged if the sum is zero. Hence in this example, the *next state vector* x' is the same as input vector x, so x is an *attractor* of the system, in this case a *fixed point* or *1-cycle*.

Of course, x in this example is just one of 2^N possible starting vectors, where N is the number of nodes in the network, and so for a 3-node network as above, there are $2^3 = 8$ possible input vectors to be operated upon by the the adjacency matrix. Let us represent these eight vectors as follows (for convenience of presentation we write them as row vectors):

$V_0 = (-1,-1,-1)$; $V_1 = (-1,-1,1)$; $V_2 = (-1,1,-1)$; $V_3 = (-1,1,1)$;

$V_4 = (1,-1,-1)$; $V_5 = (1,-1,1)$; $V_6 = (1,1,-1)$; $V_7 = (1,1,1)$.

We will use this example to illustrate two further routines which will commonly be built into such models. Taking the above updating routine to be 'Level 1', our list of routines operating at three distinct levels, is as follows:

Level 1 Procedure The above *updating routine*, using an *updating adjacency matrix*, in our present case implementing an MR procedure as a particular example;

Level 2 Procedure The *trajectory routine* - this maps the sequences of states generated by the iterative action of the matrix A on a given input state;

Level 3 Procedure The *trajectory analysis routine* - this analyses the trajectory, identifies, and outputs the corresponding *attractor* (in general a cyclic sequence of states of *length L*).

Having defined the eight starting vectors above, let us apply the trajectory, and trajectory analysis, routines to our current example. Bear in mind that for large networks, up to many hundreds of nodes in real world GRNs, analysis by computer becomes essential, but

Basin 1	**Basin 2**	**Basin 3**
V_0	V_2	
$\Downarrow$	$\Downarrow$	
$V_1 \Leftrightarrow V_1$	$V_6 \Leftrightarrow V_6$	$V_4 \Leftrightarrow V_3$
$\Uparrow$	$\Uparrow$	
V_5	V_7	

Table 6.2.7: The Three Basins of Attraction in the Toy Model System Described above

our tiny 3-node network illustrates the basic principles that apply for any value of $N \geq 1$.

Thus, simple hand calculations reveal the above three disjoint sets of vectors, constituting three attractors and their associated *basins of attraction.* (***See Figure 6.2.6 and Table 6.2.7 above.***)

The three levels of procedure enumerated above can, with further calculations, be extended to two further levels :

Level 4 Procedure The *statistical analysis routine* - for example this can test, for a large network, the effects of a sample of possible initial states (or all possible initial states in simple, low dimensional cases such as our toy model). This enables a quantitative study of the set of attractors (e.g. what proportion of the initial states is within each basin of attraction), and may allow the investigation of relationships between the properties of initial states, and their attractors.

Level 5 Procedure The *variable adjacency matrix routine* - having identified properties of interest emerging from the previous four levels, trials may be made, and hypotheses tested, by treating the adjacency (updating) matrix, A itself, as an input, and varying it in some systematic way so as to characterise which properties of A lead to which set(s) of attractors. It is to be expected that the way in which Level 5 is implemented will depend to an extent on results obtained from trialling at the lower levels.

Further analysis, by hand calculation, of the above simple example provides pointers towards the design of statistical analyses (***Level 4 above***), and towards the study (***at Level 5 above***) of how properties of the chosen adjacency matrices determine the pattern of the sets of attractors and basins generated. (Such patterns are also referred to as *state transition graphs*, or *behaviour fields* of the system in question, of which ***Table 6.2.7 above*** is a good example.)

Following through with the above simple test case, we can enumerate the number of possible 3-node, undirected, signed networks that can be constructed. There are 27 in all. However, many of these are only trivially distinct, and there are 10 nontrivially distinct classes of such networks (along with their corresponding matrices, A) amongst these.

For instance, the calculations show there to be 5 other trivially distinct networks in the same class as that constructed ***in Table 6.2.7 above***. Hence the *multiplicity* of the networks in this class is 6. As shown in this figure, this class gives rise to a pattern comprising three fixed points (three attractors in all). Two of the fixed points are fed by a basin of attraction consisting of two other state vectors, on trajectories distinct from one another. Our test vector, V_1 = (-1,-1,1), in the above example belongs to one of these classes. (***See Basin 1 in Table 6.2.7 above***.)

Further hand calculations will show that this pattern of attractors is one of five distinct such patterns that can be generated by varying the matrix A, for the class of 3-node. undirected, signed networks.

Such calculations can be extended further to show that there are two other classes of nontrivially distinct such networks which generate the same pattern of attractors as that above, and each of these classes has multiplicity 3. Examples of the corresponding matrices are :

$$A' = \begin{pmatrix} 0 & 1 & 1 \\ 1 & 0 & 0 \\ 1 & 0 & 0 \end{pmatrix} \qquad \textbf{and} \qquad A'' = \begin{pmatrix} 0 & -1 & -1 \\ -1 & 0 & 0 \\ -1 & 0 & 0 \end{pmatrix}$$

Of course the above type of analysis could be extended to larger networks, at least to a sample of appropriate adjacency matrices and input vectors, to classify which types of attractors are generated by which types of *network topology*, and by which types of *starting states* (input vectors). We see from the above summary analysis that, even such a small network can help in the formulation of questions to be asked about larger networks, in extending the algorithm to tackle problems *at Levels 4 and 5 above*.

6.3 Elaboration of Network Models in Developmental Systems

The above description outlines the basic principles of biological modelling based on networks. *In this section*, we will deal briefly with a selection of research papers, based upon topic areas of significance in the further development of network modelling in developmental systems.

6.3.1 Introduction of Random Networks and Directed Links

For the study of large networks, the need arises to use *random methods of generating networks* such as randomly generating the Boolean functions ***in 6.2.3 above***, or by building a network with *random selection of nearest neighbours to form links between nodes.*

I.Shmulevich *et al* (2002) [137], reviewed in detail the standard Boolean networks, but also include Kauffman's studies of *random Boolean networks.* In these studies, networks are generated randomly with specified classes of Boolean functions, and the effects of these on the global dynamical behaviour of the networks are studied systematically. An example of such functions is the *canalising function*, much studied by Kauffman and others, and defined formally as follows :

A Boolean function $f : \{0,1\}^n \to \{0,1\}$ is called *canalising in its ith input*, if there exist y and z such that, for all $(x_1, x_2, \ldots, x_n)$ contained in $\{0,1\}^n$ with $x_i = y$, then $f(x_1, x_2, \ldots x_n) = z$.

They also define *probabilistic Boolean networks*, where a set of *regulatory functions* is allocated to each node and, at each time step, one function from the set is chosen randomly. The dynamics in such a system can be represented as a Markov chain. Also, with the development of network theory, direct construction of the *state transition graphs*, either with *directed* or *undirected links*, became a more efficient option, without the need to generate the graphs using Boolean functions at the outset. Boolean GRNs can be defined by a directed graph, in which the nodes represent the regulatory elements (genes or their products, say) and the links represent the regulatory interactions.

Directed graphs are used in contexts other than GRNs. A.D.Sanchez *et al* [138], investigated the effect of directed links on the behaviour of a simple spin-like model evolving on a *small-world (SW) network.* Such a network results from randomly replacing a fraction p of the links in a *d-dimensional regular lattice*, with new random links. SW networks arising from such *random rewiring*, lie between the two limiting cases of *regular lattices* (where $p = 0$), and *random graphs* ($p = 1$).

This model becomes equivalent to the classic *Ising spin model* [139] when all links are undirected, but when directed links are included, *nonequilibrium phase transitions* arise, and the *phase diagram* (another term for the *behaviour field*) of the model becomes non-trivial. (***See 6.2.3 to 6.2.6 above.***) Sanchez *et al* believed that the effect of directed links may be relevant in other types of disordered network, such as *scale-free networks* (e.g. see H.Jeong (2000) [123]), and with different dynamical models : 'In trying to model real systems, directed links may play an important and unforseen role'.

This last point, and similar expectations of 'unknowns' alluded to in this section and Chapter 7, are again evocative of Thompson's key messages in Chapter 1, in particular message XII.

6.3.2 Signed Graphs, Frustration and Structural Balance

These are an elaboration of the basic graph, directed or undirected. F. Harary (1954) [140], formally defined a *signed graph*, G, as a set E of n points $\{P_1, P_2, \ldots, P_n\}$ together with two disjoint sets L^+, L^- of the set of all unordered pairs of disjoint points. The elements of the sets L^+, and L^- are called *positive links* and *negative links* respectively. A *positive cycle* of G is one in which the number of negative links is even. A *negative cycle* is not positive. The *sign of a path* in G is the product of the signs of its component links. A signed graph is *in balance* if all its cycles are positive. Harare's paper includes proofs of the following two theorems, which characterise the notion of 'balance' :

1 A signed graph is balanced if and only if for each pair of distinct points A, B all paths joining A and B have the same sign ;

2 An extension of the above, now known as *Harary's Theorem*, states that 'A signed graph is balanced if and only if its point set E can be partitioned into two disjoint subsets E_1 and E_2 in such a way that each positive link of G joins two points of the same subset, and each negative link joins two points of different subsets'.

T.Zaslavsky (1982) [141], after discussing the basic theory of signed graphs, generalised the notions of balance and switching of signed graphs, by treating these and related concepts in terms of *matroids*. In combinatorics, a matroid is a collection of subsets of a set, such that any subset of a member of the collection belongs to the collection, and such that if the

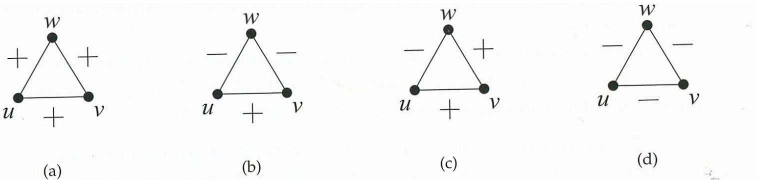

Figure 6.3.1: Frustration in possible 'triad' configurations in a signed network. In the antialignment example described in the text, only a situation where all three links are positive (as in (a)) would be stable. But this is incompatible with the requirement that the spins on neighbouring nodes should be antialigned. [From Fig.7.6, p207 of M.E.J.Newman [136], where a sociological 'friendship/animosity' situation is described, and a different interpretation of this same diagram is necessary.]

sets $\{a_1, \ldots, a_k\}$ and $\{b_1, \ldots, b_{k+1}\}$ are in the collection, then so is the set $\{a_1, \ldots, a_k, b_i\}$ for some $i \leq k+1$. This is the *exchange property*, which characterises matroids. Given any graph, the set of all sets of links containing no cycle is a matroid.

Harary's notion of 'balance' stems from the study of social networks, where a positive link denotes friendship, and a negative link denotes animosity. A *balanced network* models a stable social grouping, and an *unbalanced network* signifies instability, and the likelihood the social grouping will break up. This is similar in spirit to the notion of *frustration* in the physics of certain systems, such as *spin systems*, where the positive and negative links can model, say, forces of attraction and repulsion.

A.P.Ramirez (2003) [142], gives an intuitive description of this idea of frustration - 'the inability of a system to find a unique *ground state*'. Consider three spins (e.g. magnetic moments) which can point up or down, placed at the vertices of a triangle, with the requirement that all three spins be *antialigned* with one another.[8] This is impossible, so such an arrangement is 'frustrated'. The dynamics is also frustrated, since any spin flip will satisfy some constraints, but not others. In such cases, any unsatisfied bond is frustrated. Antialignment can be compatible with a square lattice, but on a triangular lattice no ordered pattern can satisfy all the bonds. (***See Figure 6.3.1***.) This is an instance of *geometric frustration*. ***For more on frustration, see subsection 6.4.1 below.***

6.3.3 Linking Classical Ideas of Ontogeny with Mathematical Modelling

Many papers have given attention to the linking of classical ideas such as Waddington's qualitative theory of canalisation (***see section 3.4***) to mathematical modelling. ('Canali-

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[8] In the network representation of *antialignment*, a positive link (meaning a link of attraction) joins two nodes, one 'spin-up' and the other 'spin-down'.

sation' here, is not to be confused with the mathematical definition of a Boolean canalising function - ***discussed in 6.3.1 above***.) Two such papers are from M.Siegal *et al* (2002) [143], and A.Wagner (1996) [144]. Waddington's notion of canalisation arose from embryology and genetics, and he observed - paraphrasing from [13], p21: 'There are only a certain number of defined channels along which developmental processes can go, and ... each course of development involves complex processes in which many different genes are concerned'. In [143], they model the developmental process as a network of interacting *transcriptional regulators*, and show it to constrain the genetic system to result in canalisation, even without selection towards an optimum, which is the process usually assumed to drive evolution.

There is clearly a good correspondence here (or is it an analogy or similitude?) with Thompson's belief that physical constraints are of greater significance in development than are the pressures from Darwinian selection.

In [144], Wagner again models sets of transcriptional regulators that 'mutually regulate each other's expression and thereby form stable gene *expression patterns* ... most likely subject to *strong stabilising natural selection*'. Here the idea of canalisation is embodied in the notion of *epigenetic stability.* Paraphrasing Wagner, '... the *epigenetic system* comprises 1000's of genes, expressing biologically active molecules, with regulatory interactions between them, building a *web of intracellular organisation*, and in turn a number of *intercellular communication processes* [we might now term these *intercellular signalling*], leading to *developmental coordination, and emergence of the integrated whole organism*'.

The paper then goes on to relate epigenetic stability to ideas of *developmental canalisation* and *plasticity.*

6.3.4 Use of Analytical Results in Network Modelling

Many general results have been reported in the literature, proved analytically, or demonstrated empirically, which can be useful in validating algorithms of the sorts discussed above, or variations on them.

A good example is that of A.E.Gelfand and C.C.Walker (1984) [145], who proved analytically that as the number of regulatory inputs, K, increases, an upper bound on the number of the $(2^2)^K$ functions which are canalising (***see 6.3.1 above***) is $4K(2^2)^{K-1}$. Dividing this by $(2^2)^K$ yields the fraction of Boolean functions of K variables which are canalising, and this is at a maximum for $K = 2$, and for 4 inputs this fraction drops to less than 5%.

To confirm such results, code could be written to document canalising functions for systems generated purely abstractly, by randomly choosing values of N, the number of nodes in the network (within specified limits), and K, the number of nodes providing regulatory input to each node. If the Boolean idealisation were used (***see 6.2.2***), the truth tables could be randomly populated with 1's and 0's, or if a signed network were used, the numbers of links, and their signs, could be randomly selected. On the other hand, the accepted truth of the analytic results could be used to validate appropriate code written to investigate relevant network behaviour.

6.4 Some Current Lines of Research Based on Network Models

To conclude our brief summary (*started in section 6.3 above*) of the literature in this currently very active field, let us look at some more recent research papers - published within the last ten years or so. These are chosen, and grouped by topic, to demonstrate how the Boolean approach - and models derived from it - to the modellng of GRNs (*6.2.2 and 6.2.3 above*) is currently being developed.

6.4.1 Frustration Revisited

P.-M.Binder (2008) [146] considers *dynamic frustration*, ***alluded to in 6.3.2***, and suggests that such frustration underlies the whole idea of *complexity.* Binder identifies three types of dynamical frustration :

Geometrical frustration - e.g. he refers to 'mathematical maps', which take a point in space and apply a mathematical rule to it, generating a *trajectory.* Such maps are among the simplest *deterministic rules* (or *dynamical systems*) that can lead to *chaotic behaviour* (***6.1.3 and 6.1.4 above***), generated by the frustration between tendencies of close trajectories to converge or diverge (implying folding or stretching respectively) - ***cf the logistic mapping, and the baker transformation, in 6.1.3.***

Scale frustration - arising when a system can have opposing tendencies at different scales. In our present context this may happen due to imposed *energy or fitness* *landscapes*, with peaks or valleys at many scales. These can be generated by *spin glasses*, *protein folding*, and other systems difficult to model. *Adaptive strategies* have been developed which can explore such complex landscapes with greater efficiency - such as *genetic algorithms.* e.g. J.H.Holland (1984) [147]; D.E.Goldberg (1988) [148].

Computational frustration - e.g. consider the *universal machine*, as characterised by certain *Turing machines* (***see section 5.2***). These can in principle simulate any model we may come up with, and in this sense are the most complex systems of all. Essentially, they read input, change their state, and interact with their own memory. But the more complex the machine, the more time it may spend on memory-related tasks, and at its worst, a Turing machine can enter an *infinite loop* - the famous *halting problem*, as encountered in computer science, and in the foundations of mathematics. Binder refers to this as 'dynamical frustration of the computational kind'.

In work more exclusively related to network models, G.Iacono *et al (2010)* [149], modelled large-scale biological networks represented by *signed undirected graphs* (cf the 'toy model' ***discussed in 6.2.6 above***.) In such a network, a response to a perturbation propagating through the network may lead to unpredictable and contradictory behaviour in the system. When its dynamics are always free from such contradictory reponses, the system is termed *monotone*, by analogy with a continuously increasing (or decreasing) function of one variable. The investigation of how close a biological system is to being monotone has been researched extensively in recent years. From the viewpoint of statistical physics, this problem is equivalent to testing if an *Ising model* [139], with signed interactions, has little or no frustration - corresponding to undirected cycles having an odd number of negative edges.

Iacono *et al* computed the frustration in biological networks of various types - *transcriptional, signalling, and metabolic* - ***cf 3.4 and 3.5 above***. The transcriptional work involves interactions at the *functional level* - a link in the network representing the entire action of *activation/inhibition* of a transcription factor on a target gene, thus aggregating many steps at the *molecular level.* The signalling and metabolic work is at a higher resolution, termed the *stoichiometric level.* At this level, a link represents the contribution of an individual *molecular species* to a *kinetic reaction.* The latter operates on timescales orders of magnitude smaller than at the transcriptional level.

They found that the frustration is systematically lower in transcriptional networks than in signalling and metabolic networks. A possible interpretation arises from considering *energy costs.* 'An erroneous or contradictory transcriptional action costs much more than a signalling/metabolic error, and so is to be avoided as much as possible.'

This conclusion, from a modern author, manages to combine both sides of the explanatory coin to which Thompson (and the ancient philosophers of whom he was a disciple) brought attention. On the one hand the explanation delivered by the above model is mechanical, dealing with physical and chemical principles operating on multiple scales of magnitude (both spatial and temporal); on the other, these authors could not resist the temptation to bring in an explanation based on the teleological principle - relating in this case to 'cost' and 'something to be avoided'. Thompson would have been pleased about the mechanical component in the explanation, but disparaging of the persistence, nonetheless, of the teleological explanation, which still manages to find its place to the present day! ***In our conclusions in 7.4 below, we will consider further whether the coexistence of the two principles of causation really matters (see Thompson's key messages I to V inclusive, Chapter 1), or whether it might even be a good thing, necessary for a complete understanding.***

6.4.2 Introducing Majority Rules Updating and Random Tie-breaking in Boolean Networks

C.Chaouiya *et al* (2013) [150], returned to using Boolean networks (BNs), but introduced some new ideas for constructing *the state transition rules.* In addition to the types of BNs discussed above, the paper lists numerous other variations, but in particular *Boolean threshold networks.* In these, regulatory effects are *additive*: each function is defined by a *majority rule (MR)*, whereby the activation is decided by the summation of the positive and negative inputs (possibly weighted) from the regulatory genes affecting each regulated gene. (***cf the signed network example in the' toy model', in 6.2.6***.)

The activation of each target gene will depend upon some specified *threshold* for the summation of its regulatory inputs. Such networks have been used to model control of the *cell cycle*, whereby cells involved in growth undergo periodic division into two identical, or sometimes nonidentical, *daughter cells*, which may or may not be identical to the *mother cell.* There have also been studies conducted with a subset of the ensemble of random Boolean networks (***as described in 6.3.1***), called *random Boolean threshold networks.* In these, both the regulators, and the regulatory functions, are randomly chosen.

The authors used a stochastic extension of the threshold BN, using a rule called *stochastic tie-breaking*, which associates a probability to the update value whenever the summing of the positive and negative effects alone does not decide it. Their paper discusses various MR settings, and they have compared the effects using a class of 2-gene networks which are commonly used in cell cycle models.

6.4.3 Introducing Adaptive Networks

Adaptive networks have attracted increased research attention - they are characterised by the property that changes in *network topology* (that is, in its spatial structure and organisation) and in its *dynamics*, continually feed back on one another. GRNs, for instance, are thought to optimally balance *stability* and *adaptability* by operating on, or near to *criticality* (the boundary between *order* and *chaos*) - ***see 6.1.3 to 6.1.6 inclusive***.

Much recent work focuses on the mechanisms by which adaptive networks achieve *self-organised criticality (SOC)* - see Per Bak (1996) [151]. In a directed network, each node can be considered a '*source*' or a '*sink*', depending upon the imbalance between the numbers of input and output links flowing into and out from the node. (The *in-degree* and *out-degree* respectively - e.g. see M.J.Newman (2010) [136], pp135-6.) The *net degree* of a node is the absolute difference between its in-degree and out-degree. The *imbalance* of a pair of nodes is the absolute difference between their net degrees. Many empirical ('*real world*') networks are known to contain significantly more source and sink nodes than can be expected by chance alone. Such degree imbalance leads to reduction in the number of feedback loops, and therefore enhances stability. So degree imbalance and dynamic stability are related.

This factor was exploited by B.D.MacArthur *et al* (2010) [152], by devising a signed directed graph model[9] of *adaptive regulatory networks*, using a biologically motivated *rewiring procedure*, coupled to a *stability criterion.* The construction of their network begins with a signed graph in which directions of links, and their signs, are assigned randomly, independently and with uniform probability distribution. The following rules are applied for *rewiring* at each time step, t :

- Randomly and uniformly choose a link connecting two nodes n_a and n_b such that the remaining network remains connected, along with an ordered pair of nonadjacent nodes (n_c, n_d);

- Calculate the pairwise imbalances $\mathrm{I}(n_a, n_b)$ and $\mathrm{I}(n_c, n_d)$;

- Delete the selected link, and create a new link connecting n_c and n_d, choosing its sign randomly and uniformly, and recalculate the imbalances;

- If the sum of the two imbalances after the switch is greater than before, then accept the switch unconditionally. Otherwise accept it with probability $p(t)$.

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[9] 'Graph' and 'network' are taken as synonymous here, the choice depending on the terminology used by the cited author(s). 'Graph' is the older term, and tends still to be used more by pure mathematicians.

In order to couple structural rearrangement to dynamics, $p(t)$ is allowed to vary in a manner which depends upon the changing stability of the system. In addition to the structural rewiring, each node is assumed to decay at a constant rate, which is set from $t = 0$, and applied independently, randomly and uniformly at each time step. This yields a modified adjacency matrix (***see 6.2.6***), which enables calculation of the *global stability* at each step.

The authors state that 'Previous models have shown that adaptive networks may *self-organise to a critical state*, due to rewiring based on local activity. Here, the mechanism of self-organisation is somewhat different, and relies on the fact that feedback and stability are generally inversely related. By employing a flexible rewiring scheme which allows feedback loops to be formed during periods of stability, and eliminated during periods of instability, criticality naturally arises in our model. It seems plausible that these, and other as yet unkown adaptive processes may be responsible for the criticality observed in nature'. (***cf 6.1.5, relating critical points to the idea of emergence.***)

The paper goes on to show analytically that 'the observed criticality results from the formation and breaking of *transient feedback loops* during the adaptive process'.

6.4.4 Use of Network Models in the Study of Robustness and Evolvability

Attempts have been made to formulate topological definitions of the concepts of *robustness* and *evolvability.* Robustness (also known as *resilience*) is a measure of a system's stability when subject to perturbations in its environmental inputs. Evolvability relates to the system's capacity to modify itself in response to such perturbations. Clearly these concepts have interesting parallels to the ideas of stability and adaptability (***as discussed in 6.4.3 above***).

E.Ibáñez-Marcelo *et al* (2014) [153], considered a population of cells with dynamics described by a *multiscale model*, comprising three *coupled levels*:

The microscale - entailing intracellular dynamics modelled as a GRN with directed links, this is closely related to the models used by A.Wagner [144] to study *plasticity*, and M.L.Siegal [143] *et al* to study *canalisation.* (***See 6.3.3***.) The basic idea is also similar to that of the 'toy model' ***of 6.2.6*** except that the latter was undirected. This level operates on timescales ranging from seconds to hours;

The mesoscale - comprises the population dynamics of the cells, whereby birth and death rates (*viability conditions*) are assigned according to the phenotype of each cell, operating on timescales of the order of the cellular life-span (from a few days, up to years);

The macroscale - comprising a model of the *evolutionary dynamics* of the *genotype-phenotype space (g-ps)* - see below - with timescales measured in cellular generations.

The construction of a gp-s involves a mapping between the set of viable genotypes and the set of viable phenotypes, and in graph theoretic terms this is a *bipartite graph* (comprising a mapping between two distinct classes of nodes) - e.g. see M.J.Newman (2010) [136] pp123-7. However, these authors' concept of the '*genotype-phenotype space*' is innovative in graph theory, in that it allows mappings between genotype nodes, and between phenotype nodes, as well as between genotype and phenotype nodes. They termed this a *pseudo-bipartite graph.*

Their results characterised *phenotypic robustness* by means of the *clustering coefficient* - see [136], pp199-204) - of the phenotypic nodes, and *phenotypic evolvability* as the emergence of a *giant connected component* - *ibid*, pp142 and 460-465.

6.4.5 Some Recent Analytic Work Concerning Boolean and Related Networks

To demonstrate the continuing utility and scope of analytic work in this field, I have chosen three papers, by D.Romero (2007) *et al* [154] and F.Zertuche (2009 and 2012) [155], and [156] respectively. In these papers, Boolean networks (BNs) have come to be termed *NK-Kauffman networks*, using the notation introduced by S.A.Kauffman (1993) [81]. (***See 6.2.2 and 6.2.3 above***.)

Some results arising from this work include :

1 The emergence of genetic robustness as a statistical property of the ensemble of *NK*-Kauffman networks, which imposes tight constraints on the average number of *'epistatic interactions'* that the g-ps map can have (***see 6.4.4 above***). Paraphrasing from, [81], p41, epistatic interactions are the interdependencies arising in a system of N genes, when the '*fitness contribution*'[10] of one or another allele of one gene may depend upon its interactions with the other $N-1$ genes in the system.[11]

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[10] The term '*fitness contribution*', as the name suggests, derives more from models of population genetics and evolutionary studies, than from developmental biology. It is (usually a crude and rather arbitrary) attempt to quantify to what extent a particular gene helps to ensure the survival of the organism, depending upon its interactions with other genes. It rarely derives from empirical studies, but the hope is that such models, often using *agent-based* software, can uncover general principles of gene interaction, to inform empirical and experimental work.

[11] In a sexually reproduced zygote, *homologous pairs* of chromosomes, residing in the cell nucleus, com-

2 A classification of Boolean functions on a given *NK*-Kauffman network, in terms of a new statistical property termed their *irreducible degree of connectivity* (or *Boolean irreducibility,* λ). This property has proved useful in the study of robustness against changes in connections.

3 The use of λ in the characterisation of *NK*-Kauffman network dynamics, as a function of the parameters N, K and p ($0 < p < 1$), where p is the *bias probability* that $f_i = 1$ for each of the possible 2^K arguments of a Boolean function f_i for every node i in the network. Work continues in this promising area.

This completes our brief historical survey of progress in Developmental Biology, in the century elapsed since the first publication of Thompson's *On Growth and Form* in 1917. In the final Chapter, I will attempt to bring the account up to date by considering some recent progress, in particular in the last ten years or so. In so doing, l will aim to draw conclusions about Thompson's legacy, and to judge to what extent his key messages, as spelled out in Chapter 1 above, have been vindicated.

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prise one such chromosome from each parent. On each chromosome of such a pair, any particular gene is located at its own particular *genetic locus.* Variants of the gene may occur at this locus, and the possible variants at a gene locus are called *alleles.*

CHAPTER 7

The Contemporary Synthesis in Theories of Developmental Biology - Current and Future Trends

This Chapter will assess how the historical developments outlined in Chapters 1 to 6 have impacted upon current and future trends in developmental biology.

***Sections 6.3 and 6.4 above*, illustrate how elaboration of the basic network models (*introduced in 6.2*) has enabled an approach to some of the deeply technical aspects of developmental and evolutionary biology, such as adaptation, structural stability (and adaptation), robustness, evolvability, and self-organised criticality. In so doing it demonstrates how such models can shed light on many of the issues highlighted by D'Arcy Thompson in OGF, such as the need for *explanatory principles* relating to mechanism and interconnectivity (operating on different spatial and temporal magnitudes), and the origins of ordered structures from complex systems of interacting components. This might help explain growth or differentiation, but at first sight such models, though they have a topological element to them in terms of network layout and patterns of connectivity, do not directly address the problem of 'form'. However, 'form', along with the related quality of 'structure', can be seen as a property emerging from the patterns of interaction operating between component parts of an organism, and acting at scales ranging from those of molecules, through subcellular organelles, cells, tissues and organs, up to whole**

organisms, colonies or communities thereof, or entire ecosystems.

However, it is worthwhile our briefly examining what other forms of model have been or are being tried, to address more directly and explicitly the problem of the development of form in the sense that Thompson meant it.

7.1 Reflecting on Current Developments: the Extent to which D'Arcy Thompson's Key Messages have been Vindicated

The year 2017 marked the centenary of the publication of Thompson's OGF(1), and the clearest demonstration of its lasting impact on the world of science (and many other aspects of culture) was the high profile manner in which this event was recognised and celebrated, internationally. I list here some representative examples :

I. Centenary Conference: *On Growth and Form 100*, 13-15 Oct 2017, Universities of Dundee, and St. Andrews. This interdisciplinary event, was organised by the two universities at which Thompson spent most of his career. As well as a range of presentations covering all aspects of his work, and the various fields (not necessarily scientific) influenced by it, the conference included visits to the D'Arcy Thompson Zoology Museum, Dundee (including a preview of a new exhibition exploring OGF and its legacy), and the Bell Pettigrew Museum of Natural History, St Andrews.

II. The Isaac Newton Institute (INI), Cambridge. Another key player in the OGF celebrations, the INI organised in Autumn 2017 a *Growth, Form and Self-organisation (GFS)* programme, coordinated with the above Scottish events. The INI's focus on applications of mathematics (not only to theoretical physics, but also to fields as diverse as biology, astrophysics, chemistry, computer science, engineering, environmental science, materials science, medical imaging, economics, and cryptography) made it an obvious choice to support the GFS. The workshop theme in September 2017 was *Form and Deformation in Solid and Fluid Mechanics*, and there has been a follow up workshop, *Mathematics of Form in Active and Inactive Media*, March 2019, with a focus on mathematical and physical aspects of growth, shape, and deformation in animate and inanimate systems.

III. Special edition of *Development* - the journal for advances in developmental biology and stem cells (December 2017, entitled *Special issue: On Growth and Form - 100 years on*: editorial by Thomas Lecuit, L.Mahadevan [157]). It comprises 26 articles, including an interview with Matthew Jarron, Curator of Museum Services at Dundee. All articles illustrate the modern day coupling of mathematical modelling and simulations, with quantitative experimentation: e.g. applications of topology, complex analysis, reaction-diffusion theory (derived from A.M.Turing's work [91]), graph theory and cell lineage analysis, and much more. All of this is, explicity or by implication, linked to themes developed by Thompson in OGF. The editors state: '*On Growth and Form* raised the question of the origin of biological shape in a physical framework. ... advances in our understanding of the biochemical basis of the laws of heredity have provided the modern conceptual understanding for how shapes develop anew at each generation, from a single cell - thus surviving the death of the individual through its offspring. ... [And], we are now beginning to understand how genes encode geometry. As morphology both enables and constrains function, a natural next question is how biology creates functional (and plastic) shape that begins to link morphology to physiology and behaviour.' ***Compare this latter statement with Thompson's message XII - and its corollary in 2.2, p34. This shows that we are still asking the same fundamental questions Thompson asked, but now with the benefits of enhanced knowledge (both conceptual and empirical), techniques (both computational and experimental), and technology.***

IV. ***Mathematical Intelligencer*** **articles (2018)** . These arose from the above Dundee and St. Andrews event, and comprised a brief introduction by Matthew Jarron, and papers based on the two keynotes, delivered by Evelyn Fox Keller [62], *Physics in Biology - Has D'Arcy Thompson been Vindicated?*, and Stephen Wolfram [64], *Are All Fish the Same Shape if you Stretch Them? The Victorian Tale of On Growth and Form.* These were of a broader ranging, more philosophical nature than other celebratory event outcomes above, and Wolfram's paper was also heavily biographical in content. I shall return to these papers in ***7.3.2 below***, where we look at some possible future trends.

Any reader of material relating to the above centennial events will be aware that by its nature, the content can be somewhat hagiographical, but nonetheless the volume generated constitutes an invaluable 'taking stock' of progress in the developmental sciences since Thompson's time.

7.2 Some Recent Examples of non-Network Based Developmental Models

As well as the current, highly justifiable, predilection for network-based models, there are other recently published styles of modelling which more closely reflect Thompson's interest in the physical contraints of Geometry and Topology, often in the spirit of the Platonic ideal forms which he discussed at great length in OGF. Let us elaborate further, with examples :

I. Those reflecting Platonic 'ideals' - In OGF(1), Chapter IX, *On Concretions, Spicules, and Spicular Skeletons*, (pp411-487) Thompson describes the geometry of classes of convex polyhedra - the regular*Platonic solids* (5 in number) and known to the ancients (even before Plato); the *Archimedean solids* (13 in number) described by Archimedes (in a lost work); and the more recently described *Catalan solids*, also 13 in number (often called the *Archimedean duals*) in which faces and edges are interchanged - E.Catalan (1865) [158]. In more recent work, more such solids are enumerated, in particular the *Johnson solids*, N.W.Johnson (1966) [159]. Johnson identified 92 of these, and conjectured that there were no more.

Thompson discussed in detail how *tetrahedral symmetry* appears in any close-packed aggregate of 'co-equal spheres', as in *parenchyma tissue* in plants, or the interior of a honeycomb. (e.g. Chapter VII of OGF(1), *On the Forms of Tissues or Cell Aggregates*, pp293-345.) The cube appears in the *spicular skeletons* of certain sponges, and (along with the tetrahedron) in the those of the microscopic, unicellular Radiolaria - OGF(1), Fig.231, p479. This illustration (from Haeckel's *Monograph of the Challenger Radiolaria*) also features examples of the other three Platonic solids - the regular octahedron (with triangular faces), the regular dodecahedron (pentagonal faces); and the regular icosahedron (triangular faces).

Ending his Chapter IX (in OGF(2) only)[1] Thompson declares, 'So here and elsewhere an apparently infinite variety of form is defined by mathematical laws and theorems [e.g. Euler's Law and its derivations] and *limited by the properties of space and number.*'

On p737, he states ' ... or we may go further and treat any cluster of cells, such as a segmenting ovum, as a species of polyhedron and study it from the point of view of Euler's Law and its associated theorems.' This statement fits very nicely with some recent modelling involving the mapping of *cell lineages* onto a problem in

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[1] This passage, and that below it, appear in an added section of OGF(2), pp732-740), entitled *A note on Polyhedra.*

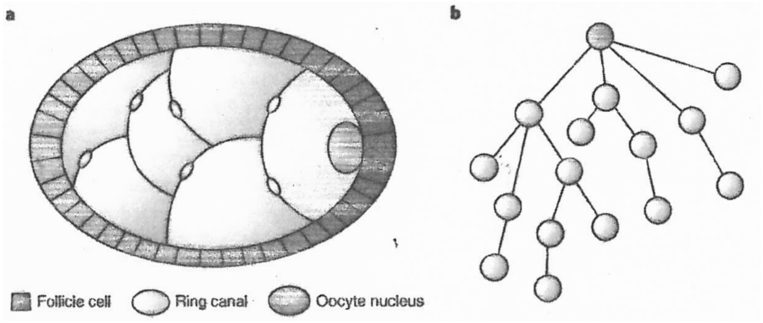

Figure 7.2.1: Tree representation of germline cell lineages in *Drosophila.* (a) Geometry of the egg chamber. (b) The cell lineage tree after the first four cell divisions. From Fig.1 in 'Connected Development', a Review in *Nature*, Ben D. MacArthur [161]

graph theory, ***which we consider next***.

II. Mapping Cell Lineage Trees (CLTs) to Johnson Polyhedra - ***Fig.7.2.1*** shows the geometry of the egg chamber of the fruit fly, *Drosophila* (left); and a graph (or network) of a special class called a *tree*, showing the relationships between the 16 *germline cells* resulting from four sets of synchronous divisions, originating with the mother cell at the top (right). The latter ultimately becomes the egg-cell (or *oocyte*), whilst the other cells become supporting *nurse cells.*

In the types of cell clustering discussed by Thompson above, the derived cells become functionally and mechanically separate after cell division, though perhaps remaining in close physical contact. However, in the above system, they remain connected (with at least some other of the cells in the CLT) by tubular cytoplasmic bridges called *ring canals* (***Fig.7.2.1***).

Rather than focusing specifically on the biochemical relations mediated by the interconnecting ring canals, I.A.Alsous *et al* (2018) [160] took the physicist's approach, asking whether the spatial arrangement of the CLT within the confined convex enclosure of the egg chamber is shaped by physical and geometrical considerations. See also B.D.MacArthur's (2018) review of this work, [161]. By comparing the adjacency structures of observed CLTs with the structures of the Platonic, Archimedean, and Johnson solids, the best fit was the Johnson solid J_{90}, also called the *disphenocingulum.*

More significantly, certain *CLT configurations* map more than others to J_{90}. So, as MacArthur mentions, 'In the language of statistical mechanics, this means that some CLT *macrostates* are realised by more *microstates*, thus establishing an *entropic principle* for their preference in development.' However, Alsous *et al* found that their CLT-J_{90} mapping was not exact, and the entropic principle did not explain sufficiently the layered structures they observed in cellular positioning. The match was improved by applying an energy-based model analogous to that of J.J.Thomson (1904) [162], in the classic problem of arranging particles with electrostatic Coulomb repulsion on a sphere.

As MacArthur observes, the physics is not necessarily enough, and ‘we must return to the approach of the biologist and dissect the molecular and cellular details, because development depends on a synergy of molecular, cellular and physical principles’.

III. Modern ‘Tests’ of Thompson’s ‘Naive Hypotheses’. Thompson was fond of proposing hypotheses based on known facts and concepts of his era. But he was not an experimentalist himself and, more seriously, this extended to his failure to report on experimental results refuting (or supporting) his hypotheses. For instance, in his Chapter XV, *On the Shapes of Eggs, and of Certain Other Hollow Structures*, pp934-57 of OGF(2), his main point (concerning birds’ eggs), derived from the popular observation that they are laid ‘blunt-end first’. From this he deduced that *peristaltic waves* in the oviduct shape the eggs ‘blunt-end-forward’. However, some had long suspected (even discussed by Needham (1931) in *Chemical Embryology*, [68], p233), that there was more to it. Finally, J.R.G.Bradfield (1951) [163], using radiographic techniques, showed that eggs pass down the oviduct pointed-end-first, and are flipped around just before emerging.

A less trivial refutation of a Thompsonian idea comes from his discussion, also in his Chapter XV, on the shape of the sea-urchin ‘shell’, or *test* in modern parlance. His ideas have been subjected to modern mathematical rigour by Alain Goriely (2018) in Chapter 8 of his new volume *The Mathematics and Mechanics of Biological Growth*, [164], further vindicating J.T.Bonner’s omission of OGF Chapter XV, from his abridged edition (1961) [5].

Thompson’s original claim, OGF2, pp945-6, was that the form of the test is exactly that of a fluid droplet resting on a flat surface. Goriely takes up this claim in his chapter on *Membranes and Shells*. Here, he formulates a rigorous mathematics of *elastic membranes*, and considers an ‘extensible axisymmetric elastic membrane filled with incompressible fluid, while neglecting shear and bending resistance’. He cites work in which a similar formulation was used to describe the shapes of red blood cells and other biomembranous stuctures. But Goriely adapts this to include effects of pressure induced stretch, gravity, bending, and geometry-dependent elastic properties of both membranes and shells based on earlier derivations.

Suffice it to say, that this is a fascinating illustration of how, when the naive hypotheses (involving analogy or similitude) which Thompson was fond of putting forward are subjected to the fierce light of modern mathematical analysis, they are likely to be found wanting. Indeed, more profound questions will arise which neither Thompson, nor even Bonner, could have imagined. e.g. from his model, Goriely concludes: 'Therefore, if [Thompson's] drop solution is indeed a valid representation of the skeleton shape in urchins, there must be both a relaxation process that constantly evolves the reference shape to the current shape, and a growth process that balances the deposition of new material in order to equilibrate the line tensions. How line tensions are being sensed and how the process is maintained and controlled during the growth of urchins remains a mystery, but one that could be partially elucidated by looking at plausible models of growth.'

In Thompson's defence it is fair to comment that, in the name of scientific progress, it is often as useful to prove an hypothesis wrong as to prove it correct.

7.3 A Brief Look at the Current, and Possible Future Trajectories of Developmental Biology

Models can be 'bottom-up', establishing general principles from studies of specific cases (often the case with Thompson's work), or the 'big picture', top-down approach, from broadly based, highly generalised theoretical constructs which yield insights into the organisation and functioning of large groups of organisms, or to the nature of life itself. (Thompson was also interested in this latter aspect.) Here, we illustrate this, while attempting to demonstrate how the same spirit in which Thompson theorised about growth and form still exists in current debate, and doubtless will be carried forward into the future of developmental biology.

7.3.1 How Do We Select Styles of Model that are 'Fit for Purpose'?

The contentious arguments are continuing now, and will continue. Thompson himself was unclear on this and, as we have seen, did not confront this question directly. So he could not even be labelled as either a reductionist or a holist. Perhaps such pluralism is valid, as it encourages a preparedness to choose whichever approach best suits the problem at hand.

I. Another dichotomy: explanation *versus* description. In the (1st edition) Preface of his now standard text *Mathematical Biology, I. An Introduction* (3rd ed., (2002) [165]), J.D.Murray makes the interesting observation that 'Mathematical descriptions are not explanations.' I suspect that many, and probably most, mathematical modellers of biological systems might take issue with this, as there is the implication here that many mathematical models are purely descriptive, and so have no explanatory value. In the Chapters above I have attempted to distinguish between purely descriptive, and explanatory models. I would suggest that 'explanation' requires some underlying system of belief, or theory, in terms of which the explanation can be expressed. For Thompson, Newtonian mechanics and statics was the theory underlying many of his explanations. (***e.g. see messages VIII to XI, Chapter 1 above***). In the early 20th century, biologists were (as now) more focused on a conceptual framework based on laws of genetics, and molecular biology, both of which of course, have quantitative as well as qualitative aspects. Increasingly, many models in biology are founded on other bodies of knowledge, such as thermodynamics, statistical mechanics, and information theory. (At the root of all such theories is explanation in terms of some 'mechanism', and its concomitant causal or multicausal chain(s).) The message here is that a mathematical model must be based upon some chosen set of foundations, ultimately the logical set theoretic foundations of mathematics itself. And such theoretical foundations evoke again the significance of analogy or similitude in the idea of 'explanation', and what informally we think of as 'understanding'. (***See Thompson's messages VI and VII.***)

'Description' in biology has a significance equal to that of 'explanation'. Just as 'explanation' is an answer to a question framed by the *interrogative* 'how' (i.e 'by what mechanism does this phenomenon come about?'), so 'description' can be embodied in answers to questions framed by other interrogatives. For example: 'what?' (e.g. morphological description); 'where?' (e.g. relative location of parts within a larger whole); 'when?' (e.g. descriptions of a chronology, or of events or stages within a time series, as in ontogeny or phylogeny); 'which' (e.g. questions requiring classificatory, or taxonomic answers - very open to set theoretic analysis.). All such 'question and answer' pairings can lend themselves to mathematical modelling, with either quantitative or qualitative outcomes (or both), though often the preference is to describe things or events in words.

Murray also asserts in his Preface that mathematics alone can never provide the complete solution to a biological problem, and offers the valuable advice that 'The best models show how a process works and then predict what may follow. If these are not already obvious to the biologists *and* the predictions turn out to be right, then you will have the biologists' attention'. (The *italics* in the above are Murray's own.)

II. The persistent ‘final *versus* mechanistic cause’ dichotomy. One important interrogative not mentioned in the account above is ‘why?’; (e.g. why has this form evolved, or what is the reason (goal or purpose) for this sequence of events ?) ***Of course, this is pertinent to the issues addressed by Thompson in his messages I to V inclusive, Chapter 1 above.)*** We have already encountered this in a number of examples - ***e.g. see under ‘fustration revisited’ in 6.4.1*** . To prove that the ‘why’ question still frequents the literature, let me cite a brief item by correspondent Colin Barras, in *New Scientist* of 03 Nov.2018, p6, entitled *Fast Evolution of Pairing Crickets.* He states ‘In 1999, researchers noticed that this strong incentive to stop singing meant that crickets in the Hawaiian island of Kaui were evolving to stay silent’. A genetic mechanism is involved, since two genes were identified which had the morphological outcome of evolving flat wings, which disabled the male crickets’ ability to produce the acoustic mating signal. Instead the females, rather than selecting males at long distance, rely on a close range tactile signal. So we see how morphological change can lead to behavioural change, and also how the teleological (why?) explanation is commonly a convenient shorthand, for a much lengthier and complicated mechanistic one. This example was induced by an invasive predator species which became a threat to noisy males.

Barras is a journalist, and is more likely than the ‘peer reviewed’ researcher to resort to the teleological explanation. Close-range acoustic signalling and mate selection in Hawaiian crickets has a long literature, and it is instructive to follow this from both the teleological and mechanistic perspectives. (e.g. see T.C..Mendelson (April 2006), [166].)

III. A modern topological analogue of the Greek ideal forms. We have mentioned René Thom’s classic text on *Structural Stability and Morphogenesis* (1975) [32] (***2.1.1 above***). Thom confronted us with an important question - is there a need for a *general theoretical biology*? C.H.Waddington, in his Forward to the first edition (in French) of the book (1972) saw it as a ‘very important contribution to the philosophy of science and to theoretical general biology in particular’. He argued that many biological processes require the use of ‘bodies of appropriate special theory’, such as ‘hydrodynamics of body fluids, the membrane permeabilities involved in nerve impulses and kidney function, the network systems of nervous connections’, etc. He regarded such theories to be limited to special aspects of biology, and hence they do not generate or apply any general principles across the subject as a whole. Most of the models in books such as Murray’s, or in mathematical biology conferences, fall into such specialised categories.

The question therefore arises: ‘Is there any need for a general theoretical biology?’ (Or at least, one applicable to biological development as a whole.) Until the 1950s, and the rise of cybernetics and systems biology, the answer was ‘probably not’.

Waddington summed it up, by perceiving that a general theory requires an *‘actual simplicity’* at some global level (e.g. treating as entities, cell types, species, muscle or nerve cells), concerning which simple rules can be identified. But this level of simplicity must come with an *unmanageable complexity* at any lower level of organisation - e.g. attempting a reductionist analysis of such entities into their basic constituents such as genes or molecules. He went on to say ‘Thom has tried to show in detail ... just how the global regularities with which biology deals can be envisaged as structures within [multidimensional] space’ and he recognised how ideas such as chreods, epigenetic landscape, and switching points (which we now call bifurcations) can be formulated in terms of *vector fields, attractors, and catastrophes.* **See 6.1.3**.

In pure mathematics, catastrophe theory is seen as a branch of *bifurcation theory*, which classifies phenomena characterised by sudden shifts in behaviour. Thom classified a special class of bifurcations into seven *elementary catastrophes.* These arise in any nonlinear system of four (or fewer) dimensionless *control parameters.* The solutions can undergo only seven distinct types of qualitative change. Many natural systems can be classified within this framework, and the results hold true, even if the form of the governing equations cannot be imagined.

We saw in Chapter 6 that the term ‘catastrophe’ has been eclipsed by the more general term, ‘bifurcation’. However, mathematicians continue to seek new classes of bifurcation types, and the chaos theorist Ralph Abraham, has created (1982-1988) what aims to be a complete encyclopedia of bifurcations [167].

A very critical paper by R.S.Zahler and H.J.Sussman (1977), *Claims and Accomplishments of Applied Catastrophe Theory* [168] contributed to its decline. They saw the mathematics as sound, and a major contribution in itself, but criticised the lack of rigour in the way it had been applied in the social and biological sciences. Thom was himself to blame in the latter respect, because of the scope of topics he had covered, including dreams, play, language, art and money. Regarding morphogenesis, Waddington himself was tentative about accepting Thom’s approach, stating in his Forward ([32]), ‘ ... [Thom] makes a bold attempt at a direct comparison between topological structure within 4-D space-time, such as ‘catastrophe hypersurfaces’, and the physical structures found in developing embryos. [However], ... he is allowing his desire to find some ‘practical results’ of his theories to push him further than he ought .... in literal interpretation of his abstract formulations’.

The theory hit its peak of popularity in the 1970s with the publication of E.C.Zeeman’s *Catastrophe Theory: Selected Papers, 1972-1977* [169]. However the popularity swiftly waned, following a review by none other than topologist Stephen Smale, discoverer of structural stability. (***See 6.1.5.***) Smale attacked not only Zeeman's, but also Thom's approach to problems outside of mathematics [170]. Smale saw Thom's theory as merely the starting point for a larger and deeper framework - that of *dynamical systems theory* (i.e. complexity theory - ***See 6.1.3***).

7.3.2 The Arrival of New Conceptualisations, and Possible New Directions

But new viewpoints are arising, and will be equally if not more contentious. Our increasing understanding of biological systems at the nanoscopic scale; the potential provided by supercomputers for greater sophistication in simulations and in 'big data' analysis; and the availability of paradigm shifting ideas in the field of Quantum Mechanics - all these are featuring in the 'leading edge' of Developmental Systems research, as within all other areas of knowledge.

I. Modelling Morphogenesis using Computer Simulation. In his keynote address to the *On Growth and Form 100* conference at Dundee (2017) alluded to ***in 7.1 above***, Stephen Wolfram [64], asked if there is a 'global theory for the shapes of fishes'. He felt that without constraints on how we stretch a fish, Thompson's geometric approach did not tell us very much. But nonetheless he said that 'just to ask the question is interesting' and the fact that OGF is full of such interesting questions along with 'curious and interesting' answers was a paradigm shift in our thinking about origins of growth and form at the macroscopic scale.

Yet progress in this regard is even nowadays limited. Wolfram asserted '... the problem is that when one looks at biological forms, they often seem far too complex to be the results of traditional mathematical equations. But starting in the 1950s a new possibility emerged: perhaps one could model biological growth [by instead using] rules like a program for a computer.'

We briefly described the basic features of Cellular Automata (CAs) ***in 5.3.5 above***. The idea first arose in the context of C.G. Langton's *'Artificial Life'* or *A-Life* (1986) [171]. E.F.Keller explains ([48], p268) that CAs exemplify the use of computers, now common in biological simulations, to explore phenomena for which neither equations nor any sort of general theory has been formulated. (There may be only rudimentary indications of the underlying dynamics of interaction.) She states, 'In such cases, what is simulated is neither a well-established set of D.E.s, nor the fundamental physical constituents (e.g. particles) of the system, but rather the observed phenomenon as seen in all its complexity - prior to simplification, [or] to any attempt to distil or reduce it to its essential dynamics.' Keller describes this as 'modelling from above.'

On this basis, the objective of such a model is [[48], p272 '...establishing *formal similitude*) [***cf Thompson's messages VI and VII***] between the outcomes of simple algorithmic procedures and the overall behaviour of the processes (be they physical, biological, economic, or other) which they are designed to explain'. But she rightly queries the success of these models, as it may be largely about presentation: 'CA models of biological systems depend [for their persuasiveness] on translating formal similitude into *visual similitude*'.

[i.e.] ... 'a good part of the appeal of CA models in biology derives from the exhibition of *computational results* in forms that exhibit a compelling visual resemblance to the processes they [claim] to represent'. **Thus, advances in *computer visualisation techniques* account in large measure for the persuasive power of CAs and similar models.** (e.g. see [48], Chapter 9, on *Synthetic Biology Redux - Computer Simulation and Artificial Life, pp269-76.*)

Another issue arises in light of our discussion above on the 'explanation *versus* description dichotomy'. Do such models contribute anything to explanation? The problem is there is ambiguity about what is to be explained in terms of what. Is it the architecture and development of computers being explained in terms of biology, or *vice versa*? Christan Jacob, in *The Art of Genetic Programming* (1999) [172], expresses doubts that CAs and their derivatives can 'help accomplish better understanding of gene-gene interactions, genotype-phenotype mappings, and epigenesis'. (See also, [48], p281.) He suggests such models may be directed more towards the design of computers that will behave more like organisms.

Nonetheless, Wolfram amongst others, persist in the use of simulations to model development and pattern formation. In his keynote address, ***7.1, p151 above***, he expressed the intention to continue his 'systematic investigation of the computational universe of possible programs [which he started in the early 1980s]'. He was 'struck by how "biological" a lot of the forms created, say, by simple [CAs] seemed.' ... '[He] kept on exploring spaces of possible programs - and discovering that the range of forms they produced seem to align ... well with the actual range of forms one sees across biological organisms.' (He looked especially at mollusc shell shapes and patterns, other pigmentation patterns, and 'various forms of plants'.)

As with Thompson, he concluded that 'the forms of organisms are not so much determined by [Darwinian evolution], as by what it is possible for processes to produce'. He considered his exploration of the 'more general space of computational processes' to be an advance on Thompson's quest for explanations by physical processes and mathematical forms.' Wolfram's results were reported in his *opus* '*A New Kind of Science*, (2002) [115].

II. How Information Couples with Matter In his recently published book *The Demon in the Machine* (2019)[2] , the quantum physicist and cosmologist Paul Davies [173], has contributed the latest to the literature on how physics can help answer the question *What is Life?*, started by Erwin Schrődinger (1944) in his book of that title [174]. In his Preface Davies states '*Patterns of information flow* can literally take on a life of their own, surging through cells, swirling around brains, and networking across ecosystems and societies, displaying their own systematic dynamics. ... It is here, in the way living systems arrange information into *organised patterns*, that the distinctive order of life emerges from the chaos of the molecular realm'.

What is implied here, is not only the way information is coded in the genetic material, and replicated, transcribed and translated in the manner discussed in ***3.4 and 3.5 above***, but also its involvement in such phenomena as *templating, scaffolding*, and the crucial roles of *assembly factors* in developmental processes (***see 6.1.2***). In the classical concept of *information* as in Shannon's theory (***4.3 above***) the information is seen as an abstract construct, distinct from any hardware involved in its processing, such as *transmitters, receivers, etc.*

In the biological system, information can be on the one hand an abstract entity, but in other situations it can take on some physical form - e.g in the processes of transcription of the DNA code into RNA, or the translation of the RNA code into polypeptide chains of amino acids, the information flow is essentially abstract. But in the process of *replication* of the DNA prior to cell division, the information in the DNA can be thought of as physical chains of nucleotides).

In this respect there is a nice analogy between information processing in biological systems, and that arising from CA models (***see I. above***), as discussed by Thomas Ray (1995) [175], pp184-5. He states that 'the "body" of a *digital organism* is the *information pattern* in memory that constitutes its machine language program. This information is *data*, but when it is passed to the computer's CPU it is interpreted as a series of *executable instructions*', and 'the bit pattern that makes up the program is the body of the "organism", but at the same time it is its complete "genetic material" [i.e. its genome].'

III. Some New Informational Concepts. These are arising in the literature, and may

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[2] 'Demon' in the title alludes to 'Maxwell's Demon' dreamed up by James Clerk Maxwell in 1867 (unpublished) - this thought experiment postulated a being whose faculties are so sharpened that he can follow every molecule in its course' [173], pp27-35.

help with developing a theory of information (and thermodynamics) as it applies to life forms, and not just to inanimate matter. For instance, *integrated information* quantifies the extent to which the whole may be greater than the sum of its parts when a system is complex. (e.g. Giullio Tononi *et al* (2016) [176], use this in developing a theory of consciousness in a physical substrate). The motivation here arises from the precept that in the history of life, each major transition (from *inanimate self-organisation, to prokaryotic cells, then eukaryotic cells, sexual reproduction, and multicellularity, and on to the origin of a central nervous system*) has come about due to reorganisation of the *informational architecture* of living organisms. Tononi posits that 'The brain is the most recent step, creating *information patterns* that think'.

Another, quite general mathematical theory (termed *effective information theory)* is being developed, investigating the effects of aggregating (e.g. by 'black-boxing') microscopic variables. (e.g. Erik Hoel (2018) [177].) He sets out to find how *agents*, with their associated *goal-directed behaviour*, can emerge from the underlying microscopic physics, which lacks these properties. (See Davies [173], pp203-4.) He concludes that there can be causal relationships that exist solely at the level of such agents. (Counter to the thinking of reductionists.)

IV. Does Quantum Theory Have a Role in Biology? In one sense, there is no doubt that it does, as all chemical phenomena are based upon quantum mechanics. However, it is the particular chemistry that is special to biologcal systems that matters here, and so the question is 'Which aspects of biochemical phenomena, specific to living systems, are dependent on which quantum mechanical laws and phenomena?'

In Chapter 5, Davies [173], he reports experimental studies suggesting a role for *quantum tunnelling* of electrons through organic molecules such as metallo-proteins (e.g. haemoglobin). It is known that enzymes connected with oxygenation, and the synthesis of the energy storing molecule ATP, depend upon the rapid transport of electrons, which is enhanced by electron tunnelling. (H. B. Gray and J.R.Winkler (2010) [178].) There is also evidence for wavelike energy transfer through quantum coherence in processes of photosynthesis in bacteria (G.S.Engel *et al* (2007) [179]). The results of these and related investigations remain speculative, but the evidence is accumulating that quantum effects do play a crucial role in distinctively molecular biological processes.

V. Has D'Arcy Thompson been Vindicated? . Davies [173], pp56-63 describes some of the 'exquisitely efficient and well-honed *nanomachines*' which, as modern research has revealed, abound within living cells. They comprise molecular scale machines and motors, mostly of protein, powered by adenosine triphosphate (ATP), the cell's internal energy storage molecule. The list includes 'motors, pumps [e.g the ionic pumps responsible for active transport of ions across the cell membrane], tubes, shears, rotors, levers and ropes.' We can argue that the existence of such mechanisms, with moving parts, capable of being driven by, and exerting physical force (on a molecular scale) is a vindication of Thompson's advocacy of the role of forces in shaping living forms.

A much studied example is the kinesin molecule, described as a freight delivery molecule, carrying cargo molecules by 'walking' along the microtubules which form a network of nanofibres criss-crossing cells. It can maintain uniform directed motion, and is thus able to overcome the random thermal motion to which it is subjected within the cellular cytoplasm. This apparently purposive behaviour, typical of such 'biomachines' is achieved because kinesin acts by a ratchet mechanism - essentially one foot at a time is always attached to its nanotubule, whilst the other moves.

E.F.Keller, in her keynote address to the *On Growth and Form 100* event (2017) at St Andrews [62], saw another vindication for Thompson's programme to be 'the role of mechanics in gene expression'. She saw the key event in the history of genetics and molecular biology to be the switch from 'the search for "genes for" particular effects (in other words, the search for genetic causation), to a focus on the regulation of gene expression, and more specifically, to the roles of *chromatin*, *epigenetic markers*, and *noncoding RNA* in this regulation'. In effect we are thinking here, of the complex relationship between genotype and phenotype. As Keller observes, 'We may claim to account for the difference between wrinkled and smooth peas ..., but where is the account of how these factors [genes] actually give rise to their effects? If genes "act", how do they act? If sequences of DNA inform, how and what do they inform?'

Only now are we learning how DNA is 'read' for protein synthesis, and that this reading depends on the DNA's conformation as a physical structure. The difference since Thompson's day is that the morphology of DNA is 'highly dynamic, and ... the processes involved operate on a molecular rather than a macro scale.'

7.3.3 Current Trends: Modern Multidisciplinary Approaches

The recent history of genetics and developmental biology - all post-dating OGF(2) (1942) - is well summed up in the MIT White Paper, *The Third Revolution: The Convergence of the Life Sciences, Physical Sciences, and Engineering*, P.A.Sharp *et al* (2011) [180]. This paper focuses on the implications to biomedical science, but its conclusions apply equally to more general research into developmental processes.

I. *The First Revolution - Molecular and Cellular Biology* : - began with the discovery of the structure of DNA (J.D.Watson and F. Crick (1953) [79]), and the mechanism of transmission of heritable characteristics. This was enhanced further by the work of F.Jacob and J.Monod (1961) [80] in establishing the role of *regulatory genes* in controlling the function of other genes, thus introducing the idea of a *genetic program*, and more recently of *gene regulatory networks (GRNs).* (***See 3.4, 3.5, 6.2, 6.3 and 6.4 for more detail.***)

For four decades, the study of cell structure and function, and their role in organismic development, was dominated by the belief that biochemistry and molecular biology were the key disciplines enabling progress in this field.

II. *The Second Revolution - Genomics* : - this built on the idea of GRNs, and established the study of a given organism's entire *genome*. This involves reading the entire DNA sequence, locating the individual genes within it, and understanding *intragenomic phenomena* (the interaction of genes across the whole genomic network).

This revolution depended upon the introduction of supercomputers into genetic research, and really took off with the funding of the *Human Genome Project* from 1990. Faster computational techniques and instrumentation allowed *gene sequencing* to be accomplished on much shorter timescales, and more cheaply, so progress accelerated. Two teams eventually published (in parallel) two *genome maps*, on almost the same day in *Nature* and *Science*, [181], [182] respectively.

As the White Paper states, 'If the molecular biology revolution enabled diseases to be understood at the molecular, 'hardware' level inside the cell, the genomics revolution enabled an understanding of the 'software' that drives the cell processes. (An analogy which would have pleased Thompson greatly! ***See messages VI and VII in Chapter 1 above.***)

III. *The Third Revolution - Convergence* : - established itself around 2005, with the emergence of ground breaking multidisciplinary research, combining molecular and cellular biology, and genomics, with the fundamentally different conceptual approaches from physical sciences and engineering, and their related technologies. This application of physical sciences to biological problems reflects Thompson's proposed programme, with particular reference to Messages VIII to XI ***as detailed in Chapter 1 above***. However, Thompson perhaps envisioned this as a one-way street from physical to biological disciplines, whereas it is emerging as a two-way process. For instance, the life sciences' understanding of complex evolutionary systems is reciprocally influencing physical science and engineering - see the White Paper [180].

7.4 Conclusions

In Chapter 1, I attempted to list (but in plainer language than Thompson himself) the key messages that he wished to convey in OGF. I have listed these as 'Messages I to XII' ***in section 1.3***. In these conclusions I wish to emphasise the continued significance of these messages to the work of theoretical, philosophical, and empirical thinkers in developmental biology. Throughout my Thesis, I have pointed out the connections between one or more of Thompson's messages, and what I consider to be key milestones in the history of the subject in the century since 1917.

I can now group the messages into subsets, which have emerged particularly since the turn of the Millennium :

a) Message XII stands on its own as an overriding theme which I believe will continue to reflect present and future approaches well. To quote again what he said ' .. in dealing with the facts of embryology or the phenomena of inheritance, the common language of the books seems to deal too much with the *material elements* concerned, as the causes of development, of variation, or of hereditary transmission.' Since he stated this, we have acquired knowledge (both empirical and conceptual) as to the nature of the *non-material elements* involved. He went on to say ' ... we may readily admit then, that besides phenomena which are obviously physical in their nature, there are actions visible as well as invisible taking place within living cells which our knowledge does not permit us to ascribe with certainty to any known physical force ... .' This of course would have sounded vitalistic to many of his contemporaries, but he averted this by concluding '... and it may or may not be that these phenomena will yield in time to the methods of physical investigation.' This continues to be a focus of research activity.

Still with Messsage XII, Thompson elaborates further, on pp154-5 of OGF(1) (***see also section 2.2 above***) that we should treat growth '... as a study which stands at the *beginning of morphological*, rather than the *end of physiological enquiry*.' In other words he perceived that growth models based on physical and/or mathematical principles alone, have a legitimate role to play, with or without our having detailed knowledge of the fabric or functioning of life. This would have been at variance with the beliefs of biologists during the period of successful progress in genetics and molecular biology in the late 20th Century, but is becoming more a focus of interest now.

b) Messages VI and VII, which concern the power of analogy, and the recognition of similitudes between living and non-living matter, form my second subset. In more modern terms we interpret this as the need for a mathematical model to be based upon some body of knowledge or theoretical foundation, not only the Newtonian mechanics which dominated Thompson's thinking, but other areas of knowledge such as thermodynamics, statistical mechanics, and information theory, about which he had scant knowledge.

c) Messages VIII to XI form my third grouping, and possibly the set of ideas which we most associate with OGF, concerning the recognition that form and growth are essentially problems in physics, and that we should move more towards establishing physico-mathematical principles, to complement the current emphasis on physico-chemical principles. (Of course our present interest in the question as to whether Quantum Theory might have a role to play, brings the physico-chemical approach back into the frame, though it is firmly based upon physical and mathematical foundations.)

Thompson's dual focus on form *versus* growth lies at the root of an apparent inconsistency in his thinking. Thompson's Theory of Transformations reflects his Platonism, as it is essentially mathematical in a *descriptive* sense, and can be treated purely mathematically without reference to causation or empirical observation. However, once he turns to problems of growth, he shifts more towards *explanation* in terms of reductionist views on the roles of forces in determining form. It is therefore difficult to characterise Thompson as exclusively 'holist' or 'reductionist' - it depends upon which approach best suits the problem being addressed.

Messages X and XI in particular, concerning Thompson's use of the terms 'force' and 'form' were the subject of much interest in the first half of the 20th Century, particularly in the empirical study of the 'relative growth of parts'. These stemmed from Thompson's most well known theory, his Theory of Transformations. However, in the main this fell foul of the trap which J.D.Murray recognises (***7.3.1***) that it failed to highlight processes which were not already obvious to biologists.

d) My final grouping comprises Thompson's key messages I to V. These essentially centre around the 'final cause *versus* mechanistic cause dichotomy', to which I have given a modern twist, based on the framing of questions using 'interrogatives' (***7.3.1 above, in particular items I and II, pp155-7***). Of course Thompson was at pains to stress the need for explanation in ways other than the teleological. But at the same time, he understood that if there is ever to be any credible account of the relation of cause and effect from the empirical point of view, there is a need to unify mechanistic and teleological principles. This in part vindicates his apparent holist/reductionist internal conflict. Philosophers still struggle with this 'ultimate causation' problem even to this day. (***Message V, p7 above.***)

7.5 A Concluding Remark

In this Thesis, we have followed a trajectory through a space of possible models (as conceived in the Cybernetics era, and framed by W.R.Ashby (1956) [88] - ***see 4.1, p63 above***). This trajectory arises from the choice (or selection) of a subset of models from Ashby's '*syntactic*', abstract space of possible models, constrained by the requirement that the models selected be applicable to the problems of biological development, growth, and the origins of form and order. This requirement was, in effect, charted out for us by D'Arcy Wentworth Thompson (in OGF(1), 1917), by positing an appropriate research programme. ***I have attempted to characterise Thompson's programme in messages I to XII, in Chapter 1 above.***

As spelled out by Ashby, and M.J.Apter (1966) [86] (***4.1***), this selective process amounts to a narrowing down of the above syntactic space to a subset (the '*semantic*' space), concerned with the naturally occurring ('real world') systems studied by empirical scientists - particularly, in our present context, in relation to developmental systems in biology.

Thompson was a follower of Aristotle, whom he considered to be the 'first biologist' and, like him, Thompson was not so much a theoretician, as the advocate of a '*metatheory*', seeking to lay down the principles by which developmental theories, and their associated models, should be constructed.

Finally I wish to highlight the following aspects of how the material is presented, as I believe they provide helpful insights into D'Arcy Thompson's (still ongoing) contributions, emanating from the publication of *On Growth and Form* in 1917 :

- A special feature is the concatenation of many historical strands of activity preceding, contemporaneous with, and subsequent to the publication of OGF, links between which have rarely, if ever, been made.

- Associated with this, the Bibliography has a wide-ranging historical dimension, spanning 1838 (J.Steiner) to 2019 (P.Davies).

- As a presentational device, I have made use of numerous dichotomies, many of which are rarely (if ever) described as such in the literature. These include my own (self-referential) 'dichotomisation *versus* unification' dichotomy, which has itself helped me to argue the case for the unification of many of the dichotomies presented (implicitly or explicitly) in the discussion. (e.g. see also the ideas of D.Lambert and A. Hughes, considered ***in 2.1.3, pp31-2***.)

I can make no claim that the particular pathway of theoretical developments I have highlighted constitutes anything like a comprehensive (and certainly not an unique or definitive) 'trajectory' through the history of the subject over the last 100 years. Clearly, the selectivity outlined above is inevitably overlain by other processes of selection, arising from my own personal experience and areas of interest, and the constraints of drafting a thesis. But nonetheless, I believe the examples I have selected reflect significant milestones, suggesting traceable links back to the thinking of D.W.Thompson, and providing signposts to future directions the subject might take.

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